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TREATMENT OF PEMPHIGUS WITH ACTH, CORTISONE AND PREDNISONE*

Results Obtained in Twenty-five Cases over a Period of Five Years

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BETWEEN 1950 and 1954, 25 patients with pemphigus were treated at the Massachusetts General Hospital with either ACTH, cortisone or prednisone. All have been followed to the time of this report, October 1, 1955, or to the time of death. The results obtained and experiences gained are presented.

REVIEW OF THE LITERATURE

Although the beneficial effects of ACTH and the corticosteroids on pemphigus are now generally known, only a few follow-up studies of patients with pemphigus thus treated have been published.[1-4]

Reymann and Søbye,[1] in 1954, reported on 12 patients followed for three years. Eight of the patients had pemphigus vulgaris, of whom 4 died of causes other than pemphigus (cachexia, nephritis, old age and cerebral hemorrhage), 2 remained well without treatment for twenty and twenty-two months, respectively, and 2 were still being treated on an ambulatory basis. Of 2 patients with pemphigus vegetans, 1 had been free of lesions for thirty-four months, and the other had shown only one vegetating lesion for the past thirteen months. Two patients with pemphigus foliaceus had not responded to ACTH in the doses administered and had died. Reymann and Søbye concluded that their results were better than those obtained by most other observers and attributed this to their different method of treatment, stating that whereas the patients of other authors had "received a high dosage of ACTH over the shortest possible period, followed, in the ambulatory stage, by maintenance doses of cortisone or ACTH, ours were treated with small doses administered in repeated courses." (We do not agree with this opinion, for reasons given below in the Discussion.)

Nelson and Brodey,[2] in 1955, reported on 27 patients with pemphigus vulgaris and 1 patient with pemphigus foliaceus treated over a period of five years. Twenty-one patients had survived, and 7 had died. Of the survivors, 19 were ambulatory; but 18 of them were still receiving treatment and only 1 was in full remission with no treatment over the past 25 months. Of the 7 deceased patients, 2 had died of pulmonary embolism during therapy, and 5 of pemphigus because of "inadequate treatment . . . as judged by our present standards." The authors stress the need of high-dosage therapy during severe exacerbations of the disease.

Frazier,[3] at the International Congress of Dermatology in 1952, reported on 20 patients with pemphigus treated at Massachusetts General Hospital. Shortly after, in 1953, a more detailed study on this group of patients was presented by Lever[4] as part of a monograph on pemphigus. This group of patients is included in the present report.

RESULTS OF TREATMENT

Clinical Results

There are two types of pemphigus, each of which has a variant: pemphigus vulgaris with pemphigus vegetans and pemphigus foliaceus with pemphigus erythematosus. The bullae of pemphigus show acantholysis (separation of epidermal cells) as a characteristic histologic feature.[4]

In pemphigus vulgaris the bullae are flaccid, break easily and leave denuded areas that tend to increase in size by progressive peripheral detachment of the epidermis. Extensive oral lesions are almost invariably present. Before the advent of ACTH and the corticosteroids, the disease was nearly always fatal. In pemphigus vegetans, in addition to bullae, pustules are present. Gradually extending verrucous vegetations form at the site of the broken bullae and pustules. The mortality before hormonal treatment was

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lower than that in pemphigus vulgaris, especially in the Hallopeau type of pemphigus vegetans in which pustules predominate over bullae. Pemphigus foliaceus also begins with flaccid bullae, but in addition, erythema, oozing and scaling are present from the beginning around the bullae as well as in other areas. Gradual extension of the lesions may lead to involvement of most, if not all, of the body surface. Oral lesions occur very rarely. The mortality, before the use of ACTH and the corticosteroids, was about 60 per cent. Pemphigus erythematosus represents either an initial phase or an abortive form of pemphigus foliaceus.

Of our 25 patients, 14 had pemphigus vulgaris, 1 had the benign type of pemphigus vegetans (Hallopeau type), and 10 had pemphigus foliaceus (Table 1). The diagnosis of pemphigus was confirmed in each case by the demonstration of acantholysis on histologic section.

Pemphigus vulgaris. Of the 14 patients with pemphigus vulgaris, 11 already had extensive lesions when treatment was started, and 3 (Cases 6, 8 and 10) still were in the initial stage (Table 1).

Present status. As of October 1, 1955, 10 patients are living, 9 of whom are ambulatory. Four patients are well: 3 of them (Cases 2, 6 and 10) have been free of lesions and without treatment for forty-nine, forty-three and twenty-five months, respectively, whereas the fourth patient (Case 4) has been free of lesions only for the past two months and is still receiving small doses of ACTH through an outside physician as a "prophylactic measure." One patient (Case 13) has a few lesions but has had no need for treatment for the past two months. Four patients (Cases 1, 7, 9 and 14) have a few lesions and are being treated on an ambulatory basis with small doses of prednisone. One patient (Case 12) is in a chronic-disease hospital because of old age associated with atherosclerosis and debility. She has a few lesions for which she is receiving small doses of prednisone.

TABLE 1. *Results of Treatment Obtained in 25 Patients with Pemphigus.*

TYPE OF PEMPHIGUS	CASE NO.	RACIAL OR NATIONAL BACKGROUND	DEGREE OF INVOLVEMENT AT START OF TREATMENT	DATE OF 1ST TREATMENT	NO. OF HOSPITAL ADMISSIONS	PERIOD OF TREATMENT IN HOSPITAL	PERIOD OF TREATMENT IN CLINIC	PERIOD OF NO TREATMENT
						mo.	*mo.*	*mo.*
Vulgaris	1*	Jewish	+ + +	Apr., 1950	12	24½	10½	30
	2*	Anglo-Saxon	+ +	Aug., 1950	3	2	2	58
	3*	Irish	+ + + +	Nov., 1950	10	20	9	25
	4*	Italian	+ + +	Jan., 1951	5	6½	46	4½
	5	Jewish	+ + +	Apr., 1951	8	6	5	9
	6	Anglo-Saxon	+	Jan., 1952	1	1	0	43
	7	Jewish	+ + +	Mar., 1952	12	15	28	7
	8	Jewish	+	June, 1952	2	1¼	26½	2
	9	Negro	+ +	July, 1952	3	2	22	14
	10	Jewish	+	May, 1953	2	1	2	25
	11	Jewish	+ +	June, 1953	2	2	2	2
	12	Jewish	+ +	Nov., 1953	5	10½	12½	0
	13	Jewish	+ + + +	Jan., 1954	2	3½	5	12½
	14	Jewish	+ + +	Oct., 1954	2	6½	5½	0
Vegetans	15*	Portuguese	+ +	May, 1950	8	3½	6½	54
Foliaceus	16*	Italian	+ + + +	May, 1950	6	5	3	56
	17*	Armenian	+ + + +	July, 1950	3	5	1	56
	18*	French Canadian	+ + +	Oct., 1950	3	5	10	5
	19*	Portuguese	+ +	Dec., 1950	3	2	0	11
	20*	Italian	+ +	June, 1951	4	5	7	39
	21*	Italian	+ + + +	Mar., 1952	4	4	4½	34½
	22	German	+ + + +	May, 1952	2	41	0	0
	23	Jewish	+ +	Sept., 1952	1	1	33	3
	24	Irish	+ +	Feb., 1953	3	4	20	9
	25	Jewish	+ +	Nov., 1953	2	2	21	0

*Cases 1-4, 15 & 16-21 previously reported as of June, 1952, as Cases 1-4, 5, 6-11, respectively, by Lever.[4]
†Patient receiving "prophylactic" treatment with small doses of hormone outside Boston.
‡Patient being cared for in chronic-disease hospital because of old age & debility.

Four patients (Cases 3, 5, 8 and 11) have died. (These cases are discussed below in the section headed "Causes of Death.") In all of them the pemphigus was well under control at the time of death.

Duration of treatment and of resultant remissions. In most of the 11 patients with extensive pemphigus vulgaris, treatment had to be given with little or no interruption for many months and even years. Often during these periods of treatment, however, the 6 and 10), after only one and three months of treatment, respectively, have been in full remission for the past forty-three and twenty-five months, respectively. The third patient (Case 8) had two brief periods of treatment in the hospital, after which she received, through an outside physician, small doses of cortisone continuously for twenty-six months until her death from cancer of the uterus. Throughout the twenty-six months she had occasionally had a few oral

TABLE 1 *(Concluded).*

TYPE OF PEMPHIGUS	CASE NO.	TOTAL PERIOD OF OBSERVATION	LONGEST PERIOD WITHOUT TREATMENT	TIME ELAPSED SINCE LAST TREATMENT	TIME ELAPSED SINCE LAST HOSPITALIZATION FOR PEMPHIGUS	DEGREE OF INVOLVEMENT ON OCT. 1, 1955, OR AT TIME OF DEATH	CONDITION OF PATIENT ON OCT. 1, 1955
		mo.	*mo.*	*mo.*	*mo.*		
Vulgaris	1*	65	13	0	6	+	Few oral & cutaneous lesions
	2*	62	55	55	57	0	Clear for 49 mo.
	3*	54	11	(Death)		+	Death from shock & hemorrhage during treatment
	4*	57	1	0†	16	0	Clear for 2 mo.
	5	20	1½	(Death)		+	Death from sepsis during treatment
	6	44	43	43	43	0	Clear for 43 mo.
	7	43	1	0	9	+	Lesions on lips & face
	8	30	2	(Death)		0	Death from carcinoma of uterus
	9	38	11	0	30½	+	Few oral lesions
	10	28	25	25	26½	0	Clear for 25 mo.
	11	6	0	(Death)		0	Death from embolism during treatment
	12	23	0	(Hospital treatment)‡		+	Few oral & cutaneous lesions
	13	21	10½	2	4	+	Lesions on scalp & forehead
	14	12	0	0	3	+	Few cutaneous lesions
Vegetans	15*	64	19	12	12	+	Few lesions on scalp & vulva
Foliaceus	16*	64	46	46	48	0	Clear for 46 mo.
	17*	62	36	36	36	0	Clear for 32 mo.
	18*	20	3	(Death)		0	Death from coronary thrombosis off treatment
	19*	13	7	(Death)		++++	Death from untreated pemphigus
	20*	51	17	12	34	0	Clear for 12 mo.
	21*	43	20	20	22½	0	Clear for 20 mo.
	22	41	0	(Hospital treatment)‡		++	Moderately extensive cutaneous lesions
	23	37	3	3	22	+	Few scattered lesions
	24	33	3	0	5	+	Few scattered lesions
	25	23	0	0	18	0	Clear for 3 mo.

*Cases 1-4, 15 & 16-21 previously reported as of June, 1952, as Cases 1-4, 5, 6-11, respectively, by Lever.[4]
†Patient receiving "prophylactic" treatment with small doses of hormone outside Boston.
‡Patient being cared for in chronic-disease hospital because of old age & debility.

amount of hormone could be reduced sufficiently to allow the patient to be treated on an ambulatory basis. The number of months each patient was treated and the number of months each patient spent in the hospital are given in Table 1.

It appears that the earlier treatment is started, the more easily the pemphigus is controlled, and the longer the period of induced remission. Three patients in whom treatment was started in the initial stage of the disease showed involution of their lesions with relatively little therapy. Two of them (Cases lesions. In contrast, only 1 of the 11 patients with extensive lesions when treatment was started (Case 2) has remained free of lesions. The other 10 required a great deal of treatment, often with large doses, and although 4 of them (Cases 1, 3, 9 and 13) at one time had prolonged remissions requiring no treatment for thirteen, eleven, eleven and ten and a half months, respectively, they then relapsed and required further treatment.

Pemphigus vegetans. The patient with the relatively benign Hallopeau type of pemphigus vegetans

(Case 15) received eight courses of ACTH, with a satisfactory response each time. As of October 1, 1955, the patient had a few pustular and vegetating lesions but had required no treatment for the past twelve months.

Pemphigus foliaceus. Of the 10 patients with pemphigus foliaceus, 4 had generalized involvement of the skin that in 3 (Cases 16, 17 and 21) was of relatively short standing — namely, eight, nineteen and three months — and in 1 (Case 22) was of long standing — namely, nine years. The other 6 patients had localized pemphigus foliaceus of one to eight months' duration (Table 1). The disease became generalized in only 1 of them (Case 19) when an outside physician withheld further treatment with hormone.

Present status. As of October 1, 1955, 8 patients were living, 7 of whom were ambulatory. Five patients were well: 3 with generalized pemphigus foliaceus (Cases 16, 17 and 21) had been free of lesions and without treatment for forty-six, thirty-two and twenty months, respectively, and 2 with localized pemphigus foliaceus (Cases 20 and 25) had been well for twelve and three months, respectively. Case 25 is still receiving small doses of prednisone, as a "prophylactic measure," from an outside physician. Two patients have a few lesions. One of them (Case 23) has been without treatment for the past three months, and the other (Case 24) is still being treated with small doses of prednisone. The patient with generalized pemphigus foliaceus of nine years' duration (Case 22) is still hospitalized. He improved considerably when large doses of ACTH were administered but relapsed whenever the dose was reduced. For the past two and a half years, he has been in a hospital for chronic diseases, where the dose has been reduced very slowly. At present he is receiving 50 mg. of cortisone daily. He has only a few skin lesions but he is remaining in the hospital because of old age and general debility.

TABLE 2. *Doses of the Various Hormone Preparations Required for the Control of Exacerbations of Pemphigus.*

TYPE OF HORMONE	ROUTE OF ADMINISTRATION	COMPARABLE DOSES		DOSE ADMINISTERED*	NO. OF EXACERBATIONS REQUIRING THIS DOSE
		RECOMMENDED INITIAL DOSE IN SEVERE CASES	RATIO		
ACTH, lyophilized	Intramuscular	300 units	15	100 units	2
				200 units	12
				300 units	5
	Intravenous for 8 hr.	40 units	2	20 units	4
				30 units	8
				40 units	18
				50 units	1
				60 units	5
				80 units	1
	Intravenous for 24 hr.	20 units	1	20 units	2
				30 units	1
				40 units	4
				80 units	1
ACTH gel	Intramuscular	240 clinical units	12	100 clinical units	1
				120 clinical units	1
				160 clinical units	3
				200 clinical units	3
				240 clinical units	3
				300 clinical units	1
Cortisone	Oral	600 mg.	30	200 mg.	3
				300 mg.	8
				400 mg.	4
				500 mg.	1
				600 mg.	1
				1500 mg.	1
Prednisone (Meticorten)	Oral	120 mg.	6	40 mg.	1
				80 mg.	2
				100 mg.	2
				120 mg.	3
				200 mg.	1

*Since ACTH intravenously given usually for severe exacerbations & cortisone by mouth for mild exacerbations, doses of various drugs administered not directly comparable, merely giving information about range of doses used.

Two patients have died (the cases are described below under "Causes of Death"). One of them (Case 18) had no lesions at the time of death. The other (Case 19) died of generalized pemphigus foliaceus while not receiving hormonal treatment.

Duration of treatment and of resultant remissions. As in pemphigus vulgaris, high doses and many months of treatment were necessary for an adequate control of the lesions, especially in the patients with generalized pemphigus foliaceus (Table 1). However, in contrast to pemphigus vulgaris, in which only 1 of 11 patients with severe involvement (Case 2) has had a long-lasting remission without relapses, all 3 patients with generalized, severe pemphigus foliaceus of recent onset (Cases 16, 17 and 21) remained free of lesions once they had cleared.

Dosage Requirements

Comparable doses. Every patient responded to treatment at all times, but very high doses were necessary for the control of some of the exacerba-

tions. It did not matter whether ACTH, cortisone or prednisone was administered, provided comparable doses were given. An approximately equivalent clinical response was observed with the following daily doses:

20 units of lyophilized ACTH as a continuous infusion.
40 units of lyophilized ACTH as an eight-hour infusion.
300 units of lyophilized ACTH intramuscularly.
240 clinical units of ACTH gel intramuscularly.
600 mg. of cortisone orally.
120 mg. of prednisone (Meticorten) orally.

Treatment of exacerbations. The dose necessary to control each exacerbation in our 25 patients is listed in Table 2. Our experience with the various preparations has been as follows:

Lyophilized ACTH, intramuscularly. Lyophilized ACTH in aqueous solution was administered intramuscularly at the beginning of this study. However, its intramuscular administration was abandoned in favor of intravenous administration for two reasons: because of the development of gluteal abscesses in 2 patients (Cases 3 and 4); and because of inadequate adrenal stimulation after its prolonged use in 2 patients (Cases 1 and 17), who then responded to intravenous infusions of ACTH.

Lyophilized ACTH, intravenously. Every patient responded to lyophilized ACTH administered as intravenous infusions. However, in several cases, continuous twenty-four-hour infusions rather than intermittent eight-hour infusions were necessary. We gained the impression that increasing the duration of the infusion from eight to twenty-four hours approximately doubled the clinical effectiveness. It also greatly increased the urinary excretion of the 17-hydroxysteroids and 17-ketosteroids (as discussed below under "Laboratory Studies"). However, the use of twenty-four-hour infusions has lately been limited to patients with severe exacerbations because this mode of administration frequently caused complications. In 2 patients (Cases 3 and 4) thrombophlebitis of the catheterized vein developed, and in 2 others (Cases 1 and 15) a staphylococcal infection occurred at the site of insertion of the catheter, which in 1 of them (Case 1) was followed by septicemia.

ACTH gel. ACTH gel was fully effective, but at the high dosage necessary for the control of severe exacerbations (160-240 clinical units a day) vertebral fractures occurred in 4 patients—Cases 1, 5, 21 and 22 (these are described below under "Side Reactions"). The prolonged action of the gel, causing continuous adrenal stimulation, was probably responsible for the osteoporosis and the resultant fractures. Therefore, ACTH gel administered daily in high doses for the treatment of exacerbations was abandoned, and its use was restricted to maintenance treatment when it was given either on alternate days or three times a week.

Cortisone. Cortisone was generally used for the treatment of minor exacerbations, but on three occasions it was given during severe exacerbations either because the patient, before the exacerbation, had received the hormone as maintenance treatment or because poor veins made the intravenous administration of ACTH difficult. All patients responded. One patient (Case 7), during a severe exacerbation, did not respond to 1000 mg. of cortisone given daily for seven days, but did so when 1500 mg. a day was given for ten days.

Prednisone. Since February, 1955, nearly all patients have been treated with prednisone (Meticorten) to test the effectiveness of this drug. It was effective when given in adequate doses, which are shown in Table 2.

Maintenance treatment. In most cases, treatment was discontinued when a remission had first been attained. However, the pemphigus became active again in all patients except 1 (Case 6), who had been treated in the very early stage of the disease. After the treatment of the second and subsequent exacerbations in the hospital, three types of maintenance programs were carried out on an outpatient basis. In Program A, the patient was given ACTH gel either on alternate days or three times a week, beginning with 160 clinical units per dose. If the clinical improvement persisted, the dose was reduced by 20 clinical units every week. At the dosage level of 40 clinical units the frequency of administration was decreased to twice a week and then to once a week before treatment was stopped. In Program B, the patient received cortisone by mouth daily, 150 mg. at first. If his condition allowed it, the dose was decreased gradually, usually by 25 mg. every week at first and, after the dose had been decreased to 75 mg. a day, by 12.5 mg. every week. In Program C, prednisone was given in a fifth of the doses indicated for cortisone.

In all three programs, whenever the patient became worse the dose was increased. When the disease could no longer be controlled adequately by maintenance doses, the patient was readmitted to the hospital for intensive treatment. In several patients (Cases 1, 3, 9, 12, 14 and 24) maintenance doses had to be given continuously for many months and in some (Cases 4, 7 and 23) even for over a year.

Laboratory Studies

Evaluation of the clinical response of the patient proved to be a much better guide to successful treatment than the study of laboratory data. Nevertheless, many laboratory tests were performed to determine the degree of induced hyperadrenocorticism.

Blood eosinophils. In most patients with pemphigus, the number of eosinophils was moderately elevated before therapy. Irrespective of the initial number of eosinophils, a good clinical response usually was not observed until the number of eosinophils had decreased below 50 per cubic millimeter. Not infrequently, the number of eosinophils decreased to 0 during periods of intensive adrenal stimulation. In several cases a dose of ACTH or cortisone, adequate to produce profound eosinopenia, was nevertheless inadequate to control the disease, and when the dose was then increased, a better clinical response occurred.

Urinary 17-ketosteroids. The urinary excretion of 17-ketosteroids before treatment was usually below normal in our patients. Whereas the normal range with the method used[5] is 5-10 mg. per twenty-four hours for females and 8-15 mg. for males, the daily excretion before treatment averaged only 2.3 mg. in 7 female patients, and 3.8 mg. in 3 male patients. At the end of the first course of ACTH the values had risen to an average of 9.2 mg. per twenty-four hours in the 7 female patients, and to 24.5 mg. in the 3 male patients.

Urinary 17-hydroxysteroids. The urinary excretion of 17-hydroxysteroids was studied according to the method of Reddy[6] in 1 patient (Case 4) during a severe exacerbation. The data indicate that a profound hyperadrenocorticoid state must be induced for the control of severe exacerbations. At first, 40 units of ACTH was administered as an eight-hour infusion daily for two weeks. No clinical improvement took place although there was considerable adrenal stimulation, as indicated by a urinary excretion of 118 mg. of 17-hydroxysteroids per twenty-four hours at the end of the two weeks. (The normal range is from 1 to 10 mg.) When the same dose was administered as a twenty-four-hour infusion daily for two weeks the excretion of 17-hydroxysteroids increased to amounts varying between 150 and 222 mg. per twenty-four hours. Simultaneously, the urinary excretion of the 17-ketosteroids rose from 39 mg. per twenty-four hours on the twelfth day of the eight-hour infusions to an average of 61 mg. during the period of twenty-four-hour infusions, and this increase was associated with prompt clinical improvement.

Side Reactions

The usual manifestations of hyperadrenocorticism, such as plethoric facies, acne, hirsutism and abnormal subcutaneous fat distribution characteristic of Cushing's disease, were seen in almost every patient. Indeed, a maximal clinical response was usually not achieved until they appeared. In several patients, however, serious or potentially serious side reactions occurred in addition as the result either of excessive hyperadrenocorticism or of the withdrawal of ACTH.

Hyperadrenocorticism. Glycosuria and hyperglycemia. Glycosuria was observed at one time or another in 16 patients and hyperglycemia in 13. None of the patients with hyperglycemia had acidosis or a decrease in the carbon dioxide content of the blood. Although at first insulin was administered to patients with hyperglycemia its use was later abandoned because of the absence of acidosis.

Vertebral fractures. In 4 patients compression fractures of vertebral bodies occurred (Table 3). Two patients (Cases 1 and 22) had a single fracture, 1 (Case 5) had 2 fractures, and 1 (Case 21) had 5 fractures. The fractures caused severe back pain but no neurologic signs. They were treated by a gradual lowering of the dose followed by omission of ACTH, bed rest and the administration of testosterone (either methyl testosterone linguets, 10 mg. daily, or testosterone propionate, 25 mg. intramuscularly three times a week). All fractures healed without sequelae except for a decrease in stature.

It is significant that in all 4 patients the vertebral fractures occurred at about the same time, in the winter and spring of 1953, when daily injections of large doses of ACTH gel were the routine method of treatment. No vertebral fractures had occurred during the preceding three years when either intramuscular injections or intravenous infusions of lyophilized ACTH or oral doses of cortisone had been administered. None have occurred since, even in patients who previously had had fractures, possibly because daily, high-dosage therapy with ACTH gel was abandoned and all patients on prolonged therapy were given testosterone prophylactically in the doses mentioned above.

Mental changes. Two patients (Cases 1 and 21) showed severe psychic disturbances, and 11 showed mild mental changes. The mild changes consisted of euphoria and restlessness, associated in 5 patients (Cases 3, 5, 7, 13 and 14) with periods of confusion. In none of the patients with mild changes was it necessary to discontinue treatment since sedation with chloral hydrate or paraldehyde proved adequate. In the 2 patients with severe psychic disturbances, treatment was discontinued temporarily.

In the first of these 2 patients (Case 1) an acute manic psychosis developed during the 8th hospital admission, while she was receiving ACTH intravenously. The psychosis subsided within 4 days after omission of ACTH. When, after the 9th admission, because of inactivity of the pemphigus, ACTH was gradually withdrawn, she became severely depressed. Electric-shock treatments were given, with considerable improvement. However, 4 months later, the depression recurred. After 14 months without hormonal therapy, further treatment of the pemphigus became necessary. Prednisone was given this time. Two months after resumption of therapy the depression grew worse and further shock treatments were administered, followed again by improvement. Since then the patient has shown some moodiness but no real depression even though on several occasions she has received further treatment with prednisone.

The 2d patient (Case 21), during his 3d course, consisting of daily injections of ACTH gel, became severely paranoid. The psychosis subsided shortly after discontinuation of therapy. During a subsequent course of ACTH no psychic changes were noted.

It is of interest that the mental changes recurred during subsequent treatment in only 1 of the 13 patients (Case 1), in whom it was doubtful if the depression was caused solely by the hormonal treatment. The possibility exists that it was largely a menopausal depression.

cular injections of ACTH. Two patients (Cases 1 and 15) receiving continuous infusions had staphylococcal infections at the catheter site, followed in 1 (Case 1) by septicemia caused by hemolytic *Staphylococcus aureus*. The infection in both patients responded to antibiotics. Another patient (Case 17)

TABLE 3. *Incidence of Side Reactions during Treatment with ACTH, Cortisone or Prednisone.*

Type of Pemphigus	Case No.	Fractures of Vertebras	Mental Changes	Bacterial Infections	Miscellaneous Effects	ACTH Withdrawal Reaction	Cause of Death
Vulgaris	1	+	+++	Catheter-site infection, with sepsis	Pulmonary tuberculosis; peptic ulcer.	+	
	2	–	–	—	—	–	
	3	–	++	Gluteal abscess; pyuria.	Coma; renal calculi; hemorrhages.	–	Shock & hemorrhage during treatment
	4	–	–	Gluteal abscess	—	–	
	5	++	++	Subcutaneous abscesses; sepsis.	—	+	Septicemia during treatment
	6	–	–	—	—	–	
	7	–	++	Gluteal abscess	—	–	
	8	–	–	—	—	–	Carcinoma during treatment
	9	–	+	—	—	–	
	10	–	–	—	—	–	
	11	–	+	—	Phlebothrombosis, with pulmonary embolism	–	Pulmonary embolism during treatment
	12	–	–	—	—	–	
	13	–	++	—	—	–	
	14	–	++	—	Hemorrhages	–	
Vegetans	15	–	–	Catheter-site infection	—	–	
Foliaceus	16	–	+	—	—	–	
	17	–	–	Pyoderma	—	–	
	18	–	–	—	—	–	Coronary thrombosis with patient off treatment
	19	–	–	—	—	–	Untreated pemphigus
	20	–	+	—	—	–	
	21	+++	+++	—	—	+	
	22	+	+	—	—	+	
	23	–	–	—	—	–	
	24	–	–	—	—	–	
	25	–	+	—	—	–	

Electrolyte imbalance. Imbalance of the serum electrolytes during hormonal treatment can usually be prevented by a diet low in sodium and the oral administration of 3-6 gm. of potassium chloride a day. Thus, a disturbance in the electrolyte balance occurred in only 1 patient.

This patient (Case 1) while receiving daily 40 units of ACTH as a continuous intravenous infusion with only 3 gm. of potassium chloride had a decrease in serum potassium to 1.8 milliequiv. per liter. There was great weakness but no loss of reflexes or electrocardiographic changes. Treatment consisted of intravenous infusions of potassium dibasic phosphate. The response was prompt.

Bacterial infections. Bacterial infections occurred in 7 patients. In 3 (Cases 3, 4 and 7) staphylococcal abscesses developed at the site of previous intramus-

had severe pyoderma in the pubic region, followed by glomerulonephritis, which subsided slowly. One patient (Case 3) had persistent pyuria associated with the formation of bilateral renal calculi.

One patient (Case 5) died of staphylococcal septicemia (this case is discussed below under "Causes of Death"). The septicemia did not respond to antibiotics, possibly because during the entire course of hormonal treatment antibiotics had been given prophylactically — a practice that we have since abandoned (as pointed out below).

Miscellaneous side reactions. Reactivation of a duodenal ulcer as well as of pulmonary tuberculosis occurred in 1 patient (Case 1). In another (Case 3) a comatose state developed.

In the 1st patient (Case 1) the duodenal ulcer caused pain but no melena. ACTH was temporarily discontinued. The ulcer healed within 6 weeks. There was only once a mild recurrence of the ulcer although the patient received vigorous hormonal therapy on many occasions.

The tuberculosis was characterized by cavitation in the upper lobe of the right lung. Treatment with ACTH was discontinued, but because of the severity of the pemphigus, it had to be resumed within 1 month. In spite of this, the cavities healed within 6 months under treatment with para-aminosalicylic acid, isonicotinic acid hydrazide and intermittent administration of streptomycin. Each time thereafter when hormonal treatment was administered some antituberculous treatment was also given.

The other patient (Case 3) was being treated with high doses of lyophilized ACTH intramuscularly. On the 27th day of treatment, without premonitory symptoms, she lost consciousness and remained comatose for 5 days, after which she gradually and completely recovered. Various tests yielded no clues to the cause of the coma. During numerous subsequent courses of treatment no significant side reactions occurred except that renal calculi and pyuria developed. During the 10th admission she suddenly died of shock associated with massive bleeding (this case is discussed further below in the section entitled "Causes of Death").

Questionable side reactions. One patient (Case 11) died of pulmonary embolism secondary to phlebothrombosis of the right leg (discussed below under "Causes of Death"). Although an increased incidence of thromboembolic complications during and immediately after the administration of cortisone and ACTH has been reported by Cosgriff, Diefenbach and Vogt[7] and by Nelson and Brodey,[2] Fahey[8] found no significant alteration in clotting time during the administration of corticotropin or cortisone.

Bleeding was observed in 2 patients, with a fatal outcome in 1.

The first of the 2 patients (Case 14) was receiving intravenous infusions of ACTH. On the 41st day of treatment the temperature rose to 102°F. for 2 days. On the following day numerous ecchymoses were noted on the lower extremities. Several large ecchymoses on the feet and knees became necrotic and formed large ulcers, which healed in the course of months. As soon as the ecchymoses had appeared, the treatment was changed from ACTH to cortisone because the possibility was considered that he had adrenal failure. One month later, while he was receiving 300 mg. of cortisone a day, the temperature rose to 103°F., and ecchymoses appeared on the ankles. After 2 days, the temperature returned to normal, and the ecchymoses gradually subsided. During both attacks several blood cultures had remained sterile. During subsequent exacerbations he received up to 200 mg. of prednisone a day, with no recurrence of the bleeding.

The 2d patient (Case 3) died of shock associated with massive bleeding while prednisone was being withdrawn (this case is discussed below under "Causes of Death").

ACTH withdrawal reaction. This type of reaction may occur when ACTH is rapidly withdrawn. It was observed 5 times in 4 patients and was characterized by pronounced weakness, depression, diarrhea and a maximum temperature of 103°F. occurring within forty-eight hours of the withdrawal of ACTH. In most cases there was also a fall in blood pressure. The electrolyte pattern and the concentration of blood sugar were normal, and there was no rise in eosinophils as in the usual hypoadrenocortical state.

The 1st patient (Case 1), during her 8th hospital admission, received daily for 3 months large doses of ACTH gel. Because the lesions had cleared, ACTH was decreased by 10 clinical units each day from 180 clinical units to 0. On the day after discontinuance of ACTH fever, drowsiness and hypotension developed. She recovered spontaneously in 1 week.

The 2d patient (Case 5) showed the withdrawal reaction in a most pronounced form. A staphylococcal septicemia developed simultaneously and caused the patient's death (this case is discussed below under "Causes of Death").

The 3d patient (Case 21) had received large doses of ACTH gel daily for nearly 2 months when a paranoid psychosis developed, as mentioned above. ACTH was withdrawn somewhat rapidly, by daily decrements of 30 clinical units, from 240 clinical units to 0. On the day after discontinuance of treatment, the patient began to have fever, diarrhea and hypotension. After 9 days, the reaction subsided. At the same time the psychosis cleared.

The 4th patient (Case 22) had a withdrawal reaction twice. The 2d reaction was recognized as such and successfully treated. The 1st reaction occurred after the patient had received infusions of ACTH daily for 59 days. Fever, weakness and diarrhea persisted for 6 days and resolved within 1 day, when, because of reactivation of the pemphigus foliaceus, ACTH was reinstituted. The 2d reaction occurred after the patient had received 240 clinical units of ACTH gel for 36 days. When fracture of a vertebra occurred ACTH was withdrawn by daily decrements of 20 clinical units. On the 2d day after omission of the drug, the patient became febrile, apathetic and incontinent of urine and feces. Cortisone, 50 mg. a day orally, and ACTH, 20 units a day as an 8-hour infusion, were given, with dramatic improvement. After 3 days the ACTH was omitted, but the cortisone was continued for another 2 weeks.

Causes of Death

Of the 6 deaths among our 25 patients, 1 can be attributed to the hormonal treatment. This patient (Case 5) died of a staphylococcal septicemia occurring during an ACTH withdrawal reaction.[9] In 2 patients a relation of the death to the hormonal treatment was suspected. One of them (Case 3) died of hemorrhages during the withdrawal of prednisone, and the other (Case 11) of pulmonary embolism during the withdrawal of cortisone. Two patients (Cases 8 and 18) died of incidental diseases, and 1 (Case 19) of pemphigus foliaceus while not receiving hormonal treatment.

Death attributable to treatment. The patient (Case 5) was being treated with large doses of ACTH. On about the 43d day of treatment 2 subcutaneous abscesses developed that the patient refused to have drained. On the 50th day, a roentgenogram revealed 2 vertebral fractures. The amount of ACTH gel was rapidly reduced from 240 clinical units a day to 120 clinical units for 1 day, 60 clinical units for 2 days and none thereafter. On the day after treatment was stopped, there was a pronounced withdrawal reaction characterized by a temperature of 102°F., weakness and stupor. Blood-pressure measurements were at times unobtainable. Three blood cultures as well as cultures from the subcutaneous abscesses grew *Staph. aureus*. On the 3d day the patient died. Autopsy revealed numerous small abscesses in the heart, lungs and kidneys from which *Staph. aureus* was cultured. The adrenal glands were greatly enlarged, weighing together 50 gm. It is likely that the septicemia occurred because of inability to localize the infection during the withdrawal reaction.

Suspected relation of death to hormonal treatment. The first of the 2 patients (Case 3), during her 1st course, had become comatose for 5 days (as mentioned above). During her 10th admission to the hospital, prednisone was given, 120 mg. a day for 1 week, 80 mg. for 5 days, 60 mg. for 5 days and 50 mg. for 25 days. The dose was then reduced

by 5 mg. every 4 days. Two days after the dose had been reduced to 5 mg. a day, the patient suddenly went into shock and died within 1 hour. A large hematoma had been noted that day over the right flank. Blood obtained just before death had shown a normal number of platelets and a normal clotting time. Autopsy revealed about 1 liter of blood in the hematoma, ecchymoses in the pleura and in the renal pelvis, and blood clots in the ureters. The stool was grossly bloody. Blood cultures obtained during autopsy were sterile. It is possible that the bleeding tendency was a side reaction of the hormone therapy and also that, although prednisone had been withdrawn slowly, adrenal insufficiency caused by the withdrawal had contributed to the patient's death.

The 2d patient (Case 11) had been treated with large doses of cortisone. On the 37th day, when the lesions had cleared and the dosage was being reduced gradually, the patient suddenly died from pulmonary embolism secondary to phlebothrombosis of the right leg, as proved by autopsy.

Incidental deaths. In the 1st patient (Case 8), death was due to carcinoma of the uterus. The 2d (Case 18) died of coronary occlusion 2 weeks after discharge from the hospital while not receiving any hormonal treatment. He had had coronary-artery disease for several years before the pemphigus.

Death from pemphigus. This patient (Case 19) died of generalized pemphigus foliaceus. On 3 hospital admissions his skin had cleared each time with treatment. When he had another relapse, he did not return but was treated elsewhere without ACTH or cortisone.

Discussion

For the treatment of severe exacerbations of pemphigus, doses of ACTH or of the corticosteroids that are much larger than those generally used in the treatment of other diseases are necessary. Most failures in the treatment of pemphigus reported in the literature are undoubtedly due to inadequate dosage. None of our patients became resistant to the hormones except to lyophilized ACTH injected intramuscularly. The fact that in some cases larger doses of hormones were required for the treatment of later exacerbations than had been required at first can be explained by the greater severity of the later exacerbations. The treatment with ACTH and the various corticosteroids has thus profoundly altered the clinical course and prognosis of pemphigus. No patient need die of pemphigus. However, the complications of the induced hyperadrenocorticoid state are similar to those occurring in spontaneously arising Cushing's syndrome and may be fatal.

Indications for Treatment

Patients with pemphigus vulgaris who were treated in the early stage of the disease required relatively small doses and subsequently had prolonged remissions, whereas those with extensive involvement required larger doses and had shorter periods of remission. In pemphigus vulgaris, therefore, early treatment is of great importance. On the other hand, in early pemphigus foliaceus, treatment can be withheld if the disease is localized and mild. However, when it is spreading, treatment should not be delayed.

Plan of Treatment

In patients requiring high doses we prefer at present to start treatment with intravenous infusions of ACTH for eight hours every day because it is our impression that this mode of treatment is least apt to produce side reactions. If a patient's veins are inadequate for intravenous infusions, one of the corticosteroids may be given by mouth instead. We believe, however, that ACTH gel should not be given daily in large doses for any length of time because of its prolonged action, which causes dangerous side reactions more readily than the intermittent action of ACTH administered intravenously for eight hours every day. For instance, compression fractures never developed when the compound was given intravenously but occurred simultaneously in 4 patients when ACTH gel was the standard treatment for exacerbations.

When the type of drug for treatment is selected it should also be remembered that a patient receiving cortisone or any other corticosteroid should not be changed over to ACTH during an exacerbation. Valuable time may be lost in such a change, since there may be a period of unresponsiveness of the adrenal glands to ACTH for seven to ten days. It is preferable to continue with the administration of corticosteroids in increased doses.

Our standard method of starting treatment is to give, depending on the severity of the case, 30-40 units of ACTH daily as an eight-hour infusion. If, after five days, new lesions continue to appear, the dose is increased to 60 units. If this amount is still inadequate, ACTH is given as a continuous twenty-four-hour infusion in doses from 40 to 80 units daily.

The initial dose, especially in severe cases, should be high enough. It is preferable to begin with too high than too low a dose. If an adequate amount is administered, improvement usually occurs within five days, and the dose can be reduced. On the other hand, if the selected dose is too low, it will have to be increased, and the length of time over which relatively high doses are administered is much greater than if adequate therapy had been administered from the beginning. This is important from the point of view of side reactions, whose development depends as much upon the length of treatment as on the dosage. We disagree with the statement by Reymann and Søbye[1] that "small doses in repeated courses" are preferable to treatment with large doses. We are convinced that if we had followed their advice many of our patients would have succumbed to the disease.

As soon as improvement is evident, the dosage should be reduced gradually. The reduction should be continued even when certain areas do not heal or a few new lesions appear as long as the disease as a whole is improving. If, during the period of gradual reduction, the disease increases in activity, the dose may have to be raised again, but, at least, the patient

has had a period during which he could recuperate from the effects of high dosage therapy. Whenever possible, one should attempt a reduction of the dosage to 0 and allow the patient a period free from treatment, even though some lesions may persist. During the period of treatment with reduced doses (maintenance treatment), we prefer to give ACTH gel on alternate days to patients whose exacerbation has been controlled with ACTH and in whom a severe recurrence of the pemphigus is anticipated. Otherwise, one of the corticosteroids is given orally.

Side Reactions

The most important rule in the prevention of serious side reactions is not to treat too long with high doses. It should never be forgotten that certain side reactions constitute a much greater risk to the patient's life than a few lesions of residual pemphigus.

Side reactions that contributed to the death of 2 patients were bacterial infection and withdrawal reactions. Since ACTH and the corticosteroids lower the resistance to infection, even minor infections require prompt attention. It is possible that drainage of the two subcutaneous abscesses in Case 5 would have prevented the staphylococcal septicemia. The routine administration of antibiotics to patients during treatment with ACTH or corticosteroids, carried out between 1950 and 1953, was abandoned because infections then arising are apt to be caused by bacterial strains resistant to antibiotics, which are then ineffective in subduing such infection. If bacterial infections arise, they should be treated promptly and vigorously with antibiotics, and, until the infection has subsided, ACTH or corticosteroids should not be withdrawn.

To prevent withdrawal reactions, ACTH and the corticosteroids, after their prolonged administration in high doses, should be withdrawn slowly, especially in the last phase, when the doses are so low as to be inadequate either, for corticotropin, to stimulate, or, for the corticosteroids, to supplant adrenal function. If any manifestations of a withdrawal reaction, such as fever, weakness, depression, diarrhea or urinary incontinence, appear, 100 mg. of cortisone or a corresponding dose of any other corticosteroid should be given immediately and, as soon as feasible, also small doses of ACTH. Both hormones should then be withdrawn gradually.

Summary and Conclusions

Since ACTH and the corticosteroids do not cure pemphigus, but merely suppress the pathologic process, the question whether permanent remissions in pemphigus occur is important. As shown by our series of patients seen before hormonal therapy,[4] pemphigus foliaceus is frequently a self-limited disease. Of the 30 patients with pemphigus foliaceus admitted to the Massachusetts General Hospital between 1936 and 1949, 12 survived, and 7 had spontaneous and permanent remissions. The remissions occurred in 2 patients after the disease had been active for two and a half years, and in the others after three, six and a half, fifteen, seventeen and twenty-six years, respectively. Pemphigus vulgaris had a much poorer prognosis than pemphigus foliaceus before hormonal treatment since in the period from 1936 to 1949 only 2 of 33 patients had permanent remissions and survived. The lesions of these 2 patients cleared after sixteen months and six years, respectively.

In the present series 3 patients with pemphigus vulgaris have been in prolonged remission for forty-nine, forty-three and twenty-five months, respectively. Four additional patients had prolonged remissions for thirteen, eleven, eleven and ten and a half months, respectively, but then relapsed. In the patients with pemphigus foliaceus the permanency of the remissions has been greater than in the patients with pemphigus vulgaris since all 4 patients with prolonged remissions of forty-six, thirty-two, twenty and twelve months, respectively, have remained free of lesions. Still, even though some patients with pemphigus vulgaris may have no full remission, they can be maintained relatively free of lesions and thus are capable of leading useful lives.

Between April, 1950, and October, 1955, 25 patients with pemphigus were treated with either ACTH, cortisone or prednisone.

Of the 14 patients with pemphigus vulgaris, 10 are living; 9 are ambulatory, and 4 of them have been in remission for forty-nine, forty-three, twenty-five and two months, respectively. Four patients have died: 1 of an incidental disease, 1 of the consequences of treatment, — namely, a staphylococcal septicemia occurring during an ACTH withdrawal reaction, — and 2 of causes possibly related to the treatment (1 of hemorrhages and the other of pulmonary embolism).

The 1 patient with pemphigus vegetans has been in remission for the past twelve months.

Of the 10 patients with pemphigus foliaceus, 8 are living; 7 are ambulatory, and 5 have been in remission for forty-six, thirty-two, twenty, twelve and three months respectively. Two patients have died, 1 of an incidental disease, and the other of generalized pemphigus foliaceus while not receiving any hormonal treatment.

Very large doses of ACTH, cortisone or prednisone are needed during severe exacerbations. We prefer for the control of exacerbations ACTH intravenously, and for maintenance treatment either ACTH gel on alternate days or one of the corticosteroids every day.

Side reactions to the hormonal treatment were common. They included mild mental changes in 11 patients and major psychoses in 2. Bacterial infections occurred in 7 patients and resulted in septicemia in 2. Vertebral fractures were observed in 4 patients, all of whom had been given daily large doses of

ACTH gel, a method of treatment since abandoned. In 4 patients the withdrawal of ACTH was followed by a reaction.

Evaluation of the clinical response proved to be a better guide to successful treatment than laboratory data.

Measurement of the urinary excretion of 17-hydroxysteroids in 1 patient indicated that a very pronounced hyperadrenocorticoid state must be induced before a severe exacerbation subsides. The same daily dose of ACTH produced a much higher excretion of 17-hydroxysteroids when given as a continuous infusion for twenty-four hours each day than when given as an intermittent infusion for eight hours daily.

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SOME OBSERVATIONS OF THE BEHAVIOR OF AMYLASE IN RELATION TO ACUTE RENAL INSUFFICIENCY*

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THE increased concentration of plasma amylase during chronic renal insufficiency has long been recognized and is considered to be a result of renal excretory failure. Plasma amylase is reported to rise in parallel with urea concentration[1] but not to heights encountered in acute pancreatitis.[2] Similar rises in amylase might be expected to accompany urea retention in *acute* renal insufficiency, but this phenomenon has received little attention.

The clinical interest in plasma amylase elevation during acute renal insufficiency is heightened by the occurrence in this condition of acute abdominal crises that may resemble acute pancreatitis. The decision to perform or defer laparotomy in a uremic patient with peritoneal irritation is especially difficult, and the finding of an elevated plasma amylase can compound the uncertainty. An encounter with such a clinical situation and subsequent observations on other patients, uremic dogs and in vitro systems are the basis of this report.

Methods

Amylase activity in plasma and urine was estimated by the method of Van Loon et al.[3] The normal range in plasma is 60-160 units per 100 ml., and that in urine 800-3200 units per twenty-four hours. Each amylase value reported is the mean of two determinations. The mean variation between duplicate analyses of urine, serum and plasma was 4.9 ± 0.7 per cent.¶ The nonprotein nitrogen was estimated by a modification of the method of Folin and Wu.[4] The Kolff rotating artificial kidney was employed in the in vivo dialyses. In vitro dialyses were performed with cellophane tubing of the same type as that used in vivo.

Case Reports

Case 1. A 22-year-old man became oliguric on July 2 after 9 days of malaise and increasing fever. Artificial-kidney dialyses were performed on July 5, 9, 13, 18 and 21. On July 23 he first complained of spasms of abdominal pain at intervals of 3 to 10 minutes. During the next three days the pains increased in severity, signs of peritonitis appeared, and his general condition became critical. The temperature was 103°F. The white-cell count was 41,800, with 97 per cent neutrophils. A blood culture was positive for *Staphylococcus aureus*. The plasma amylase was 525 units and the nonprotein nitrogen 278 mg. per 100 ml. The diagnosis was in doubt, and there was considerable speculation about the role of the disordered blood chemistry in the production of the peritoneal syndrome. Laparotomy was planned to follow modification of blood chemical abnormalities by artificial-kidney dialysis. However, the abdominal symptoms were relieved completely during the dialysis procedure. After dialysis the plasma nonprotein nitrogen was considerably lower, but the amylase remained elevated. Therefore, amylase concentrations were determined on samples of plasma and urine that had been collected and frozen during the previous 19 days when the patient had oliguria but no evidence of peritonitis (Table 1). After 30 days of oliguria diuresis occurred, and the chemical abnormalities reverted to normal. Septicemia continued, and the patient died 2 months later. Autopsy revealed bacterial endocarditis but no evidence of pancreatic disease. This patient received no opiates.

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¶Standard error of the mean.

CASE 2. A 24-year-old Negro was struck by a car on February 20, sustaining fractures of both tibias, left radius, ulna and 4 ribs and blunt trauma to the abdomen. The abdominal wall was intact, but at laparotomy the small bowel was found to be transected in 6 places. There were no gross lesions of the pancreas, and there were no signs of peritonitis after repair of the bowel. Oliguria was present from February 20, and artificial-kidney dialysis was performed on February 23 and 26 and on March 2 and 4. Diuresis began on March 9. Plasma stored for 6 months and not previously thawed yielded amylase values that were high until March 4, after which no significant elevation occurred. The nonprotein nitrogen was 164 mg. per 100 ml. on March 6 and fell gradually to normal in 4 weeks. Records are not available to determine if this patient received opiates before the third day of oliguria, but he received none subsequently (Table 2).

CASE 3. A 20-year-old boy with acute renal insufficiency had a massive hemorrhage from a lacerated superficial femoral artery on June 16. Artificial-kidney dialysis was performed on June 21, 25 and 26 for uncontrollable potassium intoxication secondary to necrotizing myositis of the leg. Plasma that had been thawed several times during 16 months' storage yielded amylase values that fell from significant elevations to nearly normal while oliguria continued and azotemia progressed. The patient died on July 1, and autopsy revealed healing tubular nephrosis and massive necrosis of muscle but no abnormality of the pancreas. This patient received 15 mg. of morphine sulfate 3 times on the day of injury, but none subsequently (Table 3).

CASE 4. A 20-year-old boy had acute renal insufficiency after traumatic amputation of the right thigh, with massive blood loss and shock, on May 3. There was no trauma to the abdomen, and no signs or symptoms pointed to intra-abdominal disorder other than renal. Artificial-kidney dialysis was performed on May 8, 12 and 16. Plasma that had been thawed several times during storage for 17 months yielded only 1 significant increase in amylase, on May 12. Diuresis began on May 18, and the plasma nonprotein nitrogen concentration started to fall on May 23. Morphine sulfate, 10 mg., was given twice on May 6, 8 and 12 and once on May 9, 18 and 21 (Table 3).

CASE 5. A 22-year-old man had acute renal insufficiency after a bullet wound of the abdomen on February 24. Perforations of the liver, right kidney and colon resulted in hemoperitoneum and peritonitis, but no specific injury to the pancreas was noted. Artificial-kidney dialysis was performed on March 3, after a 24-hour urinary output of 2090 ml., because of clinical uremia. Plasma drawn on February 26, 27, 28 and March 8, when the azotemia was severe, yielded moderate elevations of amylase after 21 months' storage with repeated thawing. The patient died on March 8, and autopsy revealed multiple abscesses, widespread necrosis and mild tubular nephrosis but no abnormality of the pancreas. This patient received no morphine (Table 3).

TABLE 1. *Levels of Nonprotein Nitrogen and Amylase in Urine and Plasma in Case 1.*

DATE	URINE VOLUME	NONPROTEIN NITROGEN			AMYLASE		
		URINE	PLASMA	URINE-PLASMA RATIO*	URINE	PLASMA	URINE-PLASMA RATIO*
	ml.	*mg./100 ml.*	*mg./100 ml.*		*mg./100 ml.*	*mg./100 ml.*	
7/6	0		125			490	
7/7	40		142				
7/8	60		222				
7/9	100		218			432	
			(Artificial-kidney dialysis)				
			164			683	
7/11	151					931	
7/12	35		295			465	
7/13	0		319			548	
			(Artificial-kidney dialysis)				
			87			526	
7/14	70	713		6.2	2455		4.6
7/15	70	695		4.6	2328		4.4
7/17	90	673		2.9	1497		2.8
7/18	150		276			536	
			(Artificial-kidney dialysis)				
			209			506	
7/19	236	675		2.9	1249		2.7
7/20	234	700		2.7	719		1.8
7/21	39	640	290			311	
	*		(Artificial-kidney dialysis)				
			76			303	
7/25	185	743		3.1	730	525	1.4
7/26	150	698	278		977	378	2.6
			(Artificial-kidney dialysis)				
			81			425	
7/28	200	610		4.7	875		

*Where urine-plasma ratio shown & values in urine & plasma not determined on same day, missing value estimated by interpolation.

Case 6. A 46-year-old man became oliguric after exposure to carbon tetrachloride vapor on April 13. Nausea and vomiting were present for the 1st 2 days, but no jaundice appeared. The serum potassium concentration did not exceed 5.6 milliequiv. per liter. The only amylase determinations were on fresh plasma before and after artificial-kidney dialysis, performed to relieve clinical uremia, on April 19 (Table 3).

Table 2. *Levels of Nonprotein Nitrogen and Amylase in Urine and Plasma in Case 2.*

Date	Urine Volume	Nonprotein Nitrogen			Amylase		
		Urine	Plasma	Urine-plasma ratio	Urine	Plasma	Urine-plasma ratio
	ml.	*mg./100 ml.*	*mg./100 ml.*		*units/100 ml.*	*units/100 ml.*	
2/23	21		278				
			(Artificial-kidney dialysis)				
2/24	81	900	111	8.	3835		
2/25	44	795	285	2.8	1095	1156	0.9
2/26	130		264		504	1388	0.4
			(Artificial-kidney dialysis)				
			135				
2/27	67	792	219	3.6			
2/28	220	592	220	2.7	481		
3/1	205	585	242	2.4			
3/2	150		325		220	496	0.4
			(Artificial-kidney dialysis)				
			131				
3/3	133	526	190	2.8	338	457	0.7
3/4	172	448	206	2.2		1272	
			(Artificial-kidney dialysis)				
			117			939	
3/5	309	421	158	2.7	165		
3/6	383	509	164	3.1	123	151	0.8
3/7	551	526	175	3.0			
3/8	823	535	193	2.8	66	128	0.5
3/9	1059	548	194	2.8	84	116	0.7
3/10	1011	553	197	2.8	77	119	0.6

Experimental Material

Dog 1 had a right-sided nephrectomy on February 12, six weeks after resection of approximately three fourths of the left kidney. Dog 2 had a bilateral nephrectomy on March 28. Dog 3 was prepared by exteriorization of both ureters, and after the wounds had healed, the ureters were clamped on February 27. Dogs 4-7 were normal (Table 4).

Results

Cases 1 and 2 had concentrations of plasma amylase that are usually considered indicative of pancreatitis. Neither patient had recognizable pancreatitis, although Case 1 had acute peritonitis that subsided completely during dialysis. The elevation of plasma amylase was present for weeks before the peritonitis appeared.

Cases 3-6 had comparable azotemia, but the amylase did not rise to levels ordinarily seen in patients with proved pancreatitis although it was abnormally elevated. The amylase determinations for the first 2 patients were done on plasma that was fresh or had not previously been thawed. The plasma for Cases 3, 4 and 5 had been thawed repeatedly before analysis for amylase. Such handling was shown to reduce amylolytic activity. However, Case 5, whose plasma was fresh when analyzed, had only mild elevation of amylase, with azotemia that was comparable with that of the other patients.

The concentration of plasma amylase did not parallel that of the nonprotein nitrogen, which rose progressively before each reduction by dialysis whereas the amylase fluctuated unaccountably. The plasma amylase concentration before and after dialysis showed no consistent directional change.

The concentration of amylase in the urine of the 2 patients so examined was highest when the volume was lowest. As the volume of urine increased, the concentration of amylase did not rise, and the total twenty-four-hour excretion of amylase fluctuated. The concentration of amylase in urine did not reflect the concentration in plasma. The urine-plasma ratio for amylase was consistently greater than unity in Case 1 and less than unity in Case 2. In both, the urine-plasma ratio for nitrogen was consistently greater than unity.

Amylase concentration was considerably increased in the plasma of the uremic dogs, but there was no apparent correlation with the degree of azotemia. Urinary amylase concentration, in the one dog in which it was examined, was not elevated at a time when plasma levels were several times normal. The urine-plasma ratio for nitrogen was greater, and that for amylase less than unity.

Discussion

It is not surprising that amylase, a constituent of urine, should accumulate in the plasma when renal function is impaired. The degree of the accumulation is surprising, since it has received little attention in the literature. Malinowski[2] has observed amylase concentrations of 370-480 units per 100 ml. in uremia, but he states that such levels have rarely interfered with interpretation. The plasma level of 1388 units per 100 ml. in Case 2 could readily be misleading, and, in fact, a lesser figure led to some hesitation when found in the patient with acute peritoneal irritation.

Myers and Killian[1] called attention to the "striking parallelism" between amylase and urea concentrations in the blood of patients with *chronic* uremia. In our patients with *acute* uremia any parallelism that might otherwise have appeared was destroyed by the reduction of nonprotein nitrogen by dialysis. During the period after dialysis the steadily rising nonprotein nitrogen was in contrast to amylase, which continued to fluctuate at high levels. Also, no consistent correlation was apparent in the dogs, which were not subjected to dialysis. The height of the plasma amylase in renal insufficiency may be related to the degree of oliguria.

Another factor that might distort a possible relation in pure excretory failure is increased production of amylase. Acute renal failure of the tubular type is often associated with trauma. In patients without renal insufficiency Howard, Frawley and Artz[5] have shown plasma amylase to be elevated after trauma to

Table 3. *Plasma Nonprotein Nitrogen and Amylase in Cases 3-6.*

Date	Urine Volume	Plasma		Date	Urine Volume	Plasma	
		Nonprotein Nitrogen	Amylase			Nonprotein Nitrogen	Amylase
	ml.	*mg./100 ml.*	*units/100 ml.*		*ml.*	*mg./100 ml.*	*units/100 ml.*
Case 3:				Case 4:			
6/18	65	106		5/6	135	121	75
6/19	80	119	487	5/7	50	189	263
6/20	90	136		5/8	60	267	
6/21	0	175	561		(Artificial-kidney dialysis)		
		184	628			67	120
	(Artificial-kidney dialysis)			5/9	85	114	
		46	426	5/10	150	132	
6/22	95	126	311	5/11	105	182	242
6/23	85	164	207	5/12	135	265	172
6/24	95	228			(Artificial-kidney dialysis)		
						106	418
				5/13	85	153	
7/1	455	315	177	5/14	140	200	130
				5/15	195	212	
				5/16	240	273	139
					(Artificial-kidney dialysis)		
							174
				5/23	1995	325	124
				5/27	3720	261	136
Case 5:				Case 6:			
2/24	365			4/19			
2/25	368			60 min. before dialysis		225	378
2/26		153	247				
2/27	850	260	378	10 min. before dialysis		213	380
2/28	1400	296	336	(Artificial-kidney dialysis)			
3/3	2090	(Artificial-kidney dialysis)		10 min. after dialysis		89	112
3/7	1185	348	386	60 min. after dialysis		73	118

the abdomen but depressed after trauma to areas remote from the pancreas. Elman[6] has reported that elevations follow surgical disorders of the abdomen not specifically involving the pancreas or its ducts. Such increments of plasma amylase have been relatively small, about enough to double the normal level, but if they occurred in a patient with impaired renal excretion, considerable elevation of the plasma level might be expected. Many such patients receive opiates, which may, by causing spasm of the sphincter of Oddi, exclude the intestinal route of excretion. As the amylase that is dammed in the pancreas is absorbed into the blood[7] the plasma level could be expected to increase further as renal function fails. Both increased production and impaired excretion may well occur in acute post-traumatic renal failure, and the latter factor also could explain the great variability of amylase levels in patients with acute pancreatitis, who sometimes have hypotension with temporary oliguria.

TABLE 4. *Results in Dogs 1-7.*

Dog No.	Date	Urine Volume	Nonprotein Nitrogen		Amylase	
			Urine	Plasma	Urine	Plasma
		ml.	*mg./100 ml.*	*mg./100 ml.*	*units/100 ml.*	*units/100 ml.*
1*	2/14	47	1620	130	19	4127
	2/15	17	2290	150	38	3006
	2/16	37	1340	167	30	3006
	2/17	158	1200	187	30	2986
	2/18	84	1608	172	32	3533
	2/21	80	800	196	17	2629
	2/23	78	1240	147	19	3144
	2/24		1365	174	10	3029
2†	3/29			120		1996
	3/30			174		2640
	4/1			293		2363
3‡	2/28			80		1644
	3/2			145		1623
4 (normal)						944
5 (normal)						1752
6 (normal)						866
7 (normal)						938

*Right kidney removed 6 wk. previously; left kidney partially resected on 2/12.

†Bilateral nephrectomy on 3/28.

‡Previously exteriorized ureters clamped on 2/27.

Case 2 had no opiates during the period of observation, but he sustained massive injury to the abdomen. After the initial period there were no symptoms and no signs suggesting intra-abdominal disorder, and it appears unlikely that continued overproduction of amylase could have been caused by the trauma. The severe chemical imbalance occurring in patients with prolonged oliguria could conceivably provoke excessive production of amylase; if this were so, it would help to explain the difference between the patient with acute oliguria and the one with chronic uremia, whose chemical imbalance is likely to be less severe.

Heifetz, Probstein and Gray[8] emphasized the ratio of the concentration of amylase in the urine to that in the plasma as a means of differentiating between excessive production and insufficient excretion. The ratio was unity or greater in all cases except those of renal disease. These authors referred to cases of acute as well as chronic renal failure in which the ratio was less than unity, but no further details were given. Case 2 and Dog 1 behaved in accordance with this concept, but the persistently elevated urine-plasma ratio of Case 1, whose renal insufficiency was unquestionable, challenges the reliability of the concept.

TABLE 5. *In Vitro Dialysis.*

Test Material	Nonprotein Nitrogen	Amylase
	mg./100 ml.	*units/100 ml.*
I. Dog plasma, 5 ml., dialyzed across cellophane into 10 ml. of Ringer's solution (pH 7.41) for 48 hr. at 7°C., with continuous agitation, & then frozen 7 days (control aliquots handled similarly but not dialyzed):		
Plasma before dialysis	28	1381
Plasma after dialysis	15	1210
Dialysate	17	0
Control aliquot		1140
Control aliquot, with 100 mg. per 100 ml. of urea added		1140
II. Human serum (Case 2), 5 ml., dialyzed across cellophane into 10 ml. of Ringer's solution (pH 7.41) for 4 hr. at room temperature, with continuous agitation, & then analyzed immediately:		
Serum before dialysis		953
Serum after dialysis		920
Dialysate		10 (neg.)
III. Human urine (Case 1) dialyzed as in II		
Urine before dialysis		2434
Urine after dialysis		2216
Dialysate		7 (neg.)

After dialysis some patients had considerably less measurable amylase, and others had more. An enzyme would not be expected to cross a cellophane membrane; yet the reductions in amylolytic activity observed in some patients after dialysis were disquieting. The activity, if not the quantity, of the enzyme might be affected by the procedure. Heparin, which was used with each dialysis, was shown not to affect the activity of amylase in vitro. An attempt was made to dialyze amylase in vitro across a membrane of known permeability to other substances in plasma (Table 5). The nonprotein nitrogen in dog plasma came into equilibrium with Ringer's solution, but no amylase crossed the membrane. The amylolytic activity of the plasma was not affected by the loss of dialyzable substances or by the addition of another

100 mg. per 100 ml. of urea. Uremic human serum was dialyzed in a different system but with similar failure of amylase to cross the membrane.

The membrane that amylase did not cross is permeable to all substances known to be filtered in quantity by the human glomerulus. The substance in urine that is measured as amylase, therefore, must have a different structure or must reach the urine by some other route. The membrane in the in vitro system was equally impermeable to urinary amylase, suggesting that renal excretion of amylase occurs by a mechanism other than glomerular filtration. It would be interesting to note whether a patient with renal disease that is predominantly glomerular would excrete amylase normally.

It is possible that certain cases of plasma amylase elevation in acute renal insufficiency reflect a mild pancreatitis. The autopsies in Case 1, 3 and 4 did not yield evidence of pancreatitis, but the possibility of lesions that had healed before death was not excluded. A review of autopsy protocols* of patients seen in Korea who died with azotemia failed to reveal any gross or histologic changes suggesting pancreatitis. Although plasma amylase was not measured in these patients, their clinical course was generally similar to that of the present patients.

*Performed at the 406th Medical General Laboratory, Far East Command, United States Army.

Summary and Conclusions

Plasma amylase concentration may be markedly elevated in some cases of acute renal insufficiency without implying an associated acute pancreatitis. Although trauma, opiates and, possibly, chemical derangements may enhance amylase concentration by increased production, the diminished urinary excretion appears to be the major cause of the protracted and exaggerated levels. When chemical and clinical uremia was modified by artificial-kidney dialysis the plasma amylase was not consistently affected and fluctuated at high levels. The urine-plasma amylase was found to vary greatly and was not therefore of diagnostic import.

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PRESENT-DAY MANAGEMENT OF PLEURAL EMPYEMA IN INFANTS AND ADULTS*

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During the past fifteen years there has been a dramatic decline in the incidence of empyema. This decrease is related to the early treatment of pneumonia with antibiotics, frequently outside hospitals and often without bacteriologic controls. However, a review of empyema and its treatment is not as outdated and impertinent as one might suppose. Cases of empyema still require hospital admission, although in reduced numbers. The patients tend to be chronically rather than acutely ill, some with complicated problems about whose treatment there is considerable diversity of opinion.

In a four-year period ending July, 1943, there were 493 admissions to the thoracic surgical section of the New Haven Hospital; of these, 82, or 16.7 per cent, represented problems in acute or chronic empyema. In 1943 penicillin began to be available for certain cases, and the rapid increase in antibiotics since then is a matter of common knowledge. In a more recent four-year period ending July, 1955, there were 1262 admissions to the same thoracic service, but only 30, or 2.4 per cent, carried the diagnosis of empyema. Thus, in twelve years, the admissions for empyema in this hospital were reduced to a seventh of the previous level.

In addition to this sharp reduction in hospital incidence, there has been a change in the relative frequency of the various pathogenic and bacterial types. Before treatment is discussed in detail, it will be necessary to consider these pathogenic trends.

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Pathogenesis

Postpneumonic Empyema

Most empyemas in the past were complications of pneumonia, commonly pneumococcal or streptococcal

in origin and less often tuberculous or staphylococcal. Postpneumonic empyema still occurs today because of delay in diagnosis, delay in treatment or inadequacy in treatment of the pneumonia. Inadequacy of treatment may comprise the use of the wrong antibiotics, or inadequate dosages of an appropriate antibiotic over too short a period.

There has been a relative increase in the incidence of staphylococcal infections of the pleura. Macaulay,[1] in discussing the experience at the Royal Edinburgh Hospital for Sick Children, reported that the relative incidence of the staphylococcal variety had advanced from 3 per cent of all empyemas in 1929 to 55 per cent in 1952. Forbes[2] found that 91 per cent of empyemas in infants under six months and 45 per cent of those under two years of age were caused by staphylococci.

It must be remembered that a postpneumonic pleural exudate usually contains a single type of bacteria. When two or more forms are demonstrable by smear or culture, one suspects the existence of a perforating abscess or other pulmonary lesion producing a pleuropulmonary fistula. The latter is an important source of difficulty in treatment and a cause of chronicity.

Postsurgical Empyema

Because of a steady increase in thoracic operations and particularly pulmonary resections this has become a relatively important group. Although the pathogenic mechanism may be simply that of bacterial contamination in a residual hemothorax or effusion, more commonly there are disruption of a bronchial, pulmonary or esophageal suture line with fistula, partial pneumothorax collapse of the lung and a continuing soilage of the pleura. Accuracy in surgical technic, adequate catheter-suction drainage of the pleural space postoperatively, effective antibiotics and the use of endotracheal aspirations to relieve atelectasis and obstructive pneumonitis have combined to reduce substantially the incidence of empyema after thoracic procedures.[3]

Post-traumatic Empyema

Penetrating stab wounds and bullet wounds as encountered in civilian practice have a low risk of complicating empyema, certainly less than 5 per cent.[4] Under military field conditions, however, pyogenic infection of large hemothorax produced by tearing, irregular shell fragments has always posed a serious therapeutic problem.

Extension from the Subdiaphragmatic Area

The extension of a subdiaphragmatic, hepatic or perinephric abscess can occur spontaneously or as the result of surgical intervention. There has been a decrease in this complication with the more effective use of broad-spectrum antibiotics in the management of intra-abdominal suppuration.

Extension from the Mediastinum and Esophagus

This type again may be spontaneous (as with perforating peptic esophagitis), traumatic (as after penetrating foreign body) or surgical. A fulminating type of tension pyopneumothorax may develop, constituting an indication for emergency surgical intervention, even in this era of antibiotics.

Treatment

The advent of the sulfonamide drugs and the antibiotics has brought changes in the therapy of empyema and has modified some concepts that were accepted as classic only twenty-five years ago. One no longer hears the terms synpneumonic (usually streptococcal) and metapneumonic (usually pneumococcal) applied to empyema. There is still concern, however, about the early bacteriologic identification of the causative organism for reasons of prognosis and proper treatment. A justifiable reluctance to perform open-drainage operations on critically ill patients with massive pleural exudates persists to the present time, not only because of the early physiologic observations of Graham and Bell[5] but also because thoracotomy is rarely required to cure an acute empyema at present.

The following appear to be guiding principles in the management of empyema:

Relief of cardiorespiratory distress by decompression of large effusions. Multiple thoracenteses may be required in some cases, but at least one aspiration is indicated for diagnostic purposes.

Control of the infection in both lung and pleural cavity by properly selected antibiotics, used systemically and topically in the empyema cavity.

Restoration of ventilatory function by natural resorption of the pleural inflammatory products or by their surgical removal (which may involve the use of aspirating needles, catheters or thoracotomy).

The goal of treatment is the obliteration of the empyema pocket by one method or another. The dictum that no empyema is safely and permanently healed until the pleural cavity is obliterated was true decades ago, and it still holds today.

Acute Postpneumonic Empyema

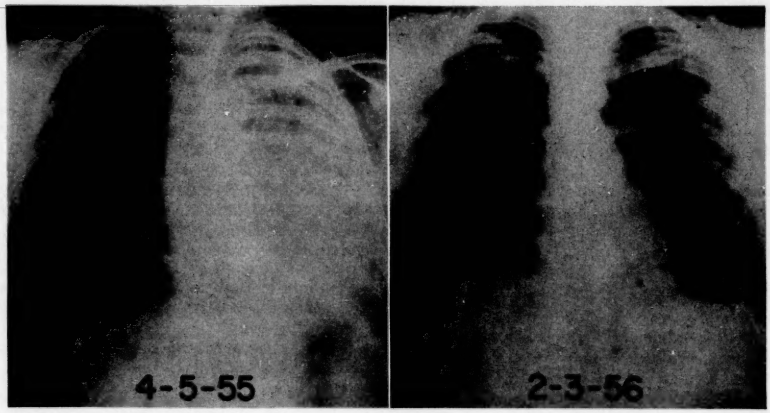
Thin, seropurulent exudates as typically caused by streptococcal or early pneumococcal infection should be managed by thoracentesis. Every attempt should be made to identify the responsible organism by smears and cultures. The latter may be difficult and slow in the wake of previous antibiotic administration. When an organism has been isolated, sensitivity

studies should guide the final choice of antibiotics, to be used systemically or topically.

Well established, thick, purulent exudates, especially when radiologically loculated, should be given a trial of enzymatic débridement with the use of streptokinase-streptodornase or trypsin. Their employment may be facilitated by the introduction of a small intercostal catheter (No. 16 to 18 Fr.) into the empyema pocket, controlled suction at a pressure of about −12 to −14 cm. of water being applied between treatments.

surgical decortication should be performed, as described below.

Extensive post-traumatic or postsurgical hemothorax, whether or not clinically or bacteriologically infected, is handled according to the same general principles. Control by thoracentesis and enzymatic débridement should be attempted unless a gross bronchial fistula or foreign body can be demonstrated. In my experience clotted hemothorax is more successfully treated by fibrinolytic enzymes than postpneumonic empyema is. In cases with inaccessible locula-



A B

FIGURE 1. *Bronchopneumonia after Measles and Empyema of Three Weeks' Duration in an Eight-Year-Old Boy.*
A=*roentgenogram of the chest on admission, showing pleurogenic scoliosis and a marked shift of the mediastinum toward the contracted left side.*
B=*roentgenogram nine months after discharge. Treatment included twelve thoracenteses with four instillations of streptokinase-streptodornase. The patient is now entirely well.*

Patients are occasionally seen with large pleural opacities remaining several weeks after antibiotic treatment even though there is no fever and the general condition is improving. There may be a history of several recent and unsuccessful thoracenteses ("dry taps"), and perhaps needle-puncture marks are still visible at the level of the eighth to tenth interspaces. By using a large-caliber needle in a higher interspace, possibly the sixth or seventh, or changing to an axillary or anterior approach, one may obtain several ounces of purulent fluid and so initiate further convalescence with enzymatic débridement and antibiotics (Fig. 1*A* and *B*).

Certain acute and subacute empyemas may be refractory to cure by the simpler methods because of early loculation, inaccessible encapsulations against the mediastinum, upon the diaphragm or between lobes, or excessive thickening of the visceral and parietal pleura, so-called pachypleuritis. In such cases tions, markedly thickened pleura, foreign bodies, and open fistula early intercostal thoracotomy and decortication should be carried out.

Staphylococcal Empyema

Staphylococcal pneumonitis can be a fulminating process of such intensity that the patient succumbs within a day or two. More commonly, it pursues a less violent course, and abscesses form about the smaller bronchi. These necrotizing areas explain the frequency of empyema and spontaneous pneumothorax in the course of the disease.

In a series of staphylococcal empyemas treated at the New Haven Hospital before 1955[6] the ages ranged from one and a half to sixteen weeks, with an average of seven weeks. The onset of the illness was recognized one to seven days before hospital admission. The average temperature at the time of entry was 38.5°C. (101.3°F.), although some much higher

levels were recorded. Certain infants were lethargic, and others restless and irritable. Dyspnea and tachypnea were frequent, but cyanosis was not common. Abdominal distention was quite prominent in about half the cases.

Although the radiologic findings are not pathognomonic, the following at least suggest a staphylococcal etiology: the occurrence of spontaneous pneumothorax; the development of pneumatoceles; rapidly changing infiltrations, with parafocal emphysema; and early loculation of the pleural exudate. A definitive diagnosis can only be made by the recovery of hemolytic *Staphylococcus aureus* from the pleural fluid or the blood. The isolation of the organism from nose and throat cultures is not diagnostic since these are positive in 60 per cent of newborn infants in hospitals.[7] When the causative staphylococci are studied for drug sensitivity, a majority are found to be resistant to penicillin in high concentrations. In the present series erythromycin and chloramphenicol appeared to be the agents to which the organisms were most often susceptible.

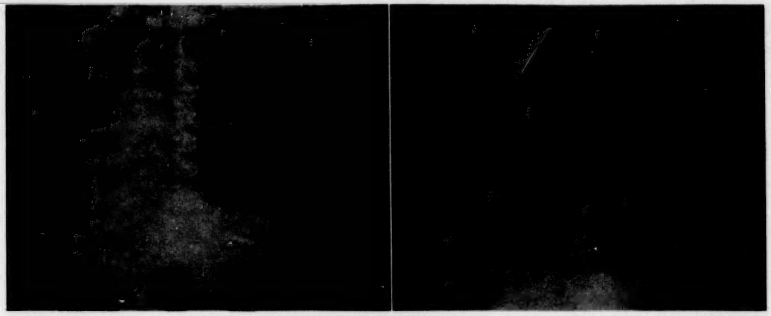


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FIGURE 2. *Staphylococcal Pneumonia and Empyema in a Two-Week-Old Infant.*
A=*roentgenogram, showing spontaneous left-sided pneumothorax demonstrated four days after admission.*
B=*roentgenogram taken after five days of intercostal suction drainage, showing re-expansion of the left lung and a large bulla developing in the right lower lobe. Complete resolution occurred with conservative treatment.*

Chief reliance in the treatment of this disease has naturally been placed on the antibiotics. However, one can depend too much on a decline in temperature and clinical improvement after initiating the drugs, and on the beneficial effects of thoracentesis. In my experience the convalescence is facilitated and made more certain by closed-suction drainage of the empyema space, with the use of small polythene tubes introduced through a large-caliber needle. These permit drainage of the pus and the introduction of antibiotics directly into the pleural space; in some cases tube drainage is an emergency requirement to control tension pneumothorax. If a small-bore polythene tube proves not to be sufficiently large one can proceed later to resect a short rib segment under local anesthesia to permit insertion of a No. 14 or 16 Fr. flexible rubber catheter. The wound is closed snugly about the tube to effect a closed system of suction drainage. Antibiotics should be maintained for ten days to two weeks after the afebrile point is reached or after the removal of the intercostal tube. Otherwise, a recurrence is likely.

The mortality in this disease before the advent of the antibiotics approached 100 per cent. Today, the prognosis is almost as good for recovery, with adequate treatment. There were no deaths in the 11 cases in the present series (all bacteriologically proved). Gagnon[8] described 47 cases with only 2 deaths, and Miller[9] 25 cases treated by early catheter drainage with no deaths.

Several points about staphylococcal empyema in the infant deserve re-emphasis. Spontaneous pneumothorax can happen at any time, even late in the course when the patient is afebrile and otherwise doing well. Therefore, equipment to cope with this emergency should be kept ready in the patient's room throughout the convalescence. Secondly, large bullae may develop even in the relatively normal lung (Fig. 2*A* and *B*). These should not be considered an indication for surgical excision, or even needle aspiration, unless they are producing a definite mechanical compression of the trachea or main bronchi. The bullae or pneumatoceles are presumably caused by valving of air in inflamed peripheral bronchi while the pneumonitis prevents the decompressive effects of collateral respiration.[10] The changes are largely reversible as the pneumonitis clears, and surgery is superfluous. The same statement can be made for the pleural densities remaining after suction drainage. If the patient is doing well clinically and the organ-

ism is under control, the pachypleuritis should be given every opportunity to resorb spontaneously. None of the present cases and only 1 of Gagnon's 47 required decortication. It seems that the keynote of late treatment of these very young infants is patience and restraint.

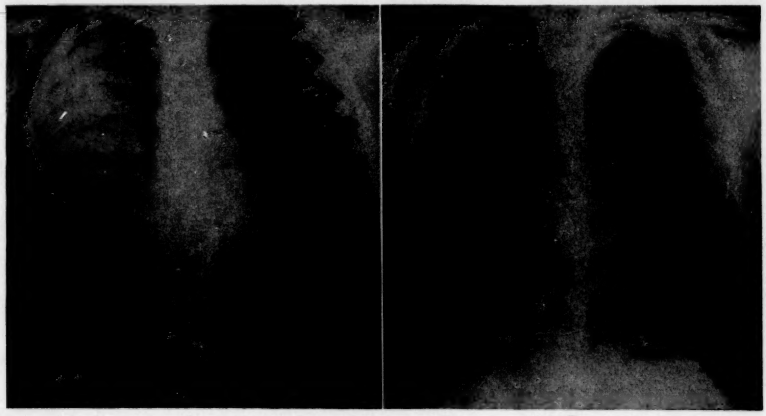
Chronic Empyema

In cases of chronic empyema it is important to rule out specific or nonspecific diseases in the underlying pulmonary parenchyma. These include neoplasms, abscess, bronchiectasis, tuberculosis, fungous infections and actinomycosis. The patient should ordinarily be subjected to diagnostic bronchoscopy and bronchography before the definitive treatment of the empyema is approached, because a simultaneous attack on associated chronic pulmonary lesions may be required.

In 1943 4 cases were reported[11] in which pulmonary resection had been accomplished in the presence of a complicating chronic empyema as a single-stage operation — that is, without preliminary drainage. Three of the 4 cases represented perforations of chronic abscess in the middle lobe and were treated by resection of the middle lobe. The fourth was a case of primary epidermoid carcinoma complicated by a Type 3 pneumococcal empyema of two months' duration and managed by total pneumonectomy. Despite the fact that only sulfonamide drugs were then available all 4 patients eventually recovered, and the patient with cancer lived for ten years, dying of heart disease at the age of seventy-four.

It is now generally accepted that the appropriate treatment of chronic empyema complicating an irreversible parenchymal lesion of the lung is a single-stage excision of the empyema pocket, usually by extrapleural dissection with simultaneous removal of the pulmonary disease by segmental resection, lobectomy or pneumonectomy as the situation demands. Pleuropneumonectomy is especially indicated when a mixed pyogenic-tuberculous empyema is associated with bronchopleural fistula, the ipsilateral lung being the seat of far-advanced fibrocaseous or cavernous disease, and the contralateral lung free of active disease or susceptible of control by antibiotics.[12] This operation abruptly terminates the toxic effects of the pleural sepsis and the possibility of aspiration of infected material from the empyema space into the good lung. The convalescence is much shorter, and the condition of the chest wall much more satisfactory than after the employment of tube drainage and multiple-stage Schede thoracoplasty.

Fortunately, many chronic empyemas are not associated with significant parenchymal disease, but result simply from inadequacies in the management of the acute phase. Delays in diagnosis and treatment, improper use of the antibiotics, imperfect drainage, fistulas and, rarely, foreign bodies contribute to chronicity. In empyemas of this type it is usually wise to perform a definitive thoracotomy after ap-



A B

FIGURE 3. *Postpneumonic Chronic Empyema in a Seven-Year-Old Boy Transferred for Surgical Treatment Fourteen Weeks after the Onset of the Illness.*
A=*roentgenogram of the chest on admission.*
B=*repeat film about a year after evacuation of empyema by thoracotomy with decortication. The patient was entirely well at the last report in 1954.*

propriate diagnostic and supportive measures. The contents of the empyema cavity are evacuated. The thickened inflammatory membrane, both parietal and visceral, is excised, including whenever possible the interlobar, mediastinal and diaphragmatic aspects of the involved pleura. The pleural space is then drained with two intercostal catheters. These are allowed to remain until the total drainage from each tube is less than 50 ml. daily and any air leaks have ceased (Fig. 3*A* and *B*).

It must be freely admitted that the procedure of empyema excision and decortication in cases of long standing is in varying degrees unsatisfactory. Over certain areas the inflammatory membrane may be inseparably united to the subpleural and interlobular connective tissue. The lung may be the site of interstitial fibrosis in a partly collapsed state and difficult to re-expand by any physiologic pressures. This reluctance to expand is abetted by the production of many tiny air leaks as the pleural dissection progresses. Nonetheless, the procedure is worthy of a trial, perhaps not so much with the hope of complete functional restitution as with the objective of obliterating the major part of the empyema space, especially in the apical half of the chest. Any basilar pocket remaining after several weeks of catheter drainage can be dealt with subsequently by the modified Schede thoracoplasty procedure, which has been described by Heller,[13] Wangensteen,[14] Grow[15] and others. In this method multiple rib segments are removed, to an extent sufficient to encompass the outlines of the empyema cavity. Through long incisions in the periosteal beds of the removed ribs, the underlying thickened pleura is excised in sections. The intact intercostal bundles are then allowed to repose directly upon the lung; the operative wound is closed with slip drainage and pressure dressings. In contrast to the traditional Schede extirpations of rib, intercostal bundle and thickened parietal pleura en bloc, the modified procedure has the great advantages of avoiding anesthesia and atony of the upper abdomen and of permitting some rib regeneration and eventual stabilization of the decostalized area. The modified Schede operation, of course, can be employed as a primary therapeutic procedure in cases of very old empyema when there is little or no possibility of functional recovery by pulmonary re-expansion.

In conclusion, some mention must be made of the important role of physiotherapeutic measures in recovery from chronic empyema and in control of the scoliotic deformities that are a particular threat in the child and adolescent.[16]

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NOVOBIOCIN IN THE TREATMENT OF SURGICAL INFECTIONS DUE TO STAPHYLOCOCCI AND OTHER GRAM-POSITIVE BACTERIA*

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NOVOBIOCIN (Cathomycin) is a new antibiotic isolated from cultures of *Streptomyces spheroides*[1] and effective in vitro against a variety of gram-positive bacteria.[2,3] Among the gram-positive micro-organisms the staphylococci are particularly sensitive to the action of this antibiotic. Of special interest is its reported efficacy against strains of staphylococci resistant to other antibiotics.

The present report deals with the in vitro antimicrobial activity of novobiocin and its efficacy in the treatment of a variety of surgical infections due

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to staphylococci and other gram-positive bacteria largely resistant, in vitro and in patients, to other antibiotics. This series includes for the most part patients who had previously received other antibiotics that proved ineffective, as well as others treated with the new antibiotic exclusively.

TABLE 1. *Sensitivity of Various Strains within a Bacterial Species to Novobiocin.**

SPECIES	NO. OF STRAINS TESTED	CONCENTRATION OF NOVOBIOCIN*		
		0.1-6.25 microgm./ml.	*12.5-25.0 microgm./ml.*	*50 & over microgm./ml.*
Hemolytic coagulase-positive *Staphylococcus aureus*	28	24	3	1
Hemolytic coagulase-negative *Staph. aureus*	2	1		1
Nonhemolytic coagulase-positive *Staph. aureus*	3	2	1	
Hemolytic coagulase-positive *Staph. albus*	2	1	1	
Hemolytic coagulase-negative *Staph. albus*	4	2	2	
Nonhemolytic coagulase-negative *Staph. albus*	1	1		
Beta-hemolytic streptococci	7	3	1	3
Alpha-hemolytic streptococci	5	5		
Gamma-hemolytic streptococci	4	3	1	
Beta-hemolytic enterococci	3	2		1
Alpha-hemolytic enterococci	4	2		2
Gamma-hemolytic enterococci	3	2		1
D. pneumoniae	4	4		
C. diphtheriae	3	3		
Esch. coli	10			10
A. aerogenes	12			12
Ps. aeruginosa	10			10
Ps. fluorescens	12	2	3	7
P. vulgaris	4		1	3
P. morganii	3		2	1
P. mirabilis	2		2	

*In last clear tube after 24 hr.

IN VITRO STUDIES

One hundred and twenty-six strains of gram-positive and gram-negative micro-organisms — staphylococci (40), streptococci (16), enterococci (10), *Diplococcus pneumoniae* (4), *Corynebacterium diphtheria* (3), *Escherichia coli* (10), *Aerobacter aerogenes* (12), *Pseudomonas aeruginosa* (10), *Ps. fluorescens* (12) and *Proteus vulgaris* (9), including bacteria freshly isolated from patients, as well as stock strains of hemolytic coagulase-positive staphylococci, resistant to penicillin, the three tetracyclines, erythromycin and sulfonamides (Table 1) — were tested for sensitivity in vitro by a twofold serial tube-dilution method.[4] The concentrations of novobiocin ranged from 50 to 0.1 microgm. per milliliter of nutrient broth. Each tube was inoculated with a bacterial suspension of approximately 10^6 bacteria obtained by dilution of an eighteen-hour to twenty-four-hour broth culture of the particular strain to be tested. Bacteria with fastidious growth requirements such as pneumococci and certain beta-hemolytic streptococci that require enriched mediums for growth were tested in nutrient broth to which sterile horse serum* (10 per cent) was added. The results of all tests were read after twenty-four hours and again after forty-eight hours of incubation.

In reading the tubes, the last two or three tubes that remained grossly clear after twenty-four hours of incubation usually became very cloudy on reincubation for an additional twenty-four hours and one or two of the last clear tubes after incubation for forty-eight hours were shown by subcultures on agar plates still to contain a few viable bacteria. This indicated that, in vitro, novobiocin is a bacteriostatic drug similar in action to the tetracyclines.

Gram-Positive Bacteria

The results confirm the reports that strains of staphylococci, as well as other gram-positive bacteria, are sensitive to novobiocin. Thirty-one staphylococcal strains were inhibited by concentrations ranging from 0.1 to 6.25 microgm. per milliliter. Most of these strains were inhibited by 0.25 microgm. or less. Seven of the 40 strains tested required 12.5-25.0, and only 2 required 50 microgm. per milliliter or more. The 12 stock strains of hemolytic coagulase-positive *Staph. aureus* resistant to all other antibiotics were all inhibited by concentrations of novobiocin ranging from 0.1 to 3.2 microgm. per milliliter. Eleven of 16 strains of streptococci (alpha, beta and gamma hemolytic) were inhibited by concentrations ranging from 0.2 to 12.5 microgm. per milliliter. Three strains of beta-hemolytic streptococci required 50 microgm. Of the 10 strains of enterococci, 6 were inhibited by 0.8-6.25 microgm. per milliliter, and 4 required 50 microgm. or more. All diphtherial and pneumococcal strains were inhibited by 3.2 microgm. or less.

Gram-Negative Bacteria

All strains of *Esch. coli* (10), *A. aerogenes* (12) and *Ps. aeruginosa* (10) and 7 of 12 strains of *Ps. fluorescens* required 50 microgm. per milliliter or more of the drug for inhibition of growth. Two strains of *Ps. fluorescens* were inhibited by 0.8 and 1.6 microgm. respectively. Five of 9 proteus strains were in-

*With the latter strains the antibacterial action of novobiocin may have been partially suppressed since a richer medium may interfere with the action of an antibiotic.[4]

hibited by 12.5 to 25 microgm., whereas 4 grew well at 50-200 microgm. per milliliter.

Comment

Novobiocin was extremely effective in vitro against most strains of staphylococci and streptococci, and was especially useful against staphylococci resistant to other antibiotics. Except for some strains of *P. mirabilis* and *Ps. fluorescens* the drug was not effective against the gram-negative bacilli tested.

Clinical Observations

Thirty patients (Table 2) with a variety of surgical infections received novobiocin. Twenty-three patients had failed to respond to previous antibiotic therapy (penicillin alone in 8 cases, penicillin and streptomycin in 4, penicillin and tetracycline in 2, local bacitracin ointment in 2, penicillin and erythromycin in 2, penicillin, streptomycin and chlortetracycline in 1, tetracycline in 1, a sulfonamide and penicillin in 1, a sulfonamide and tetracycline in 1 and penicillin, chlortetracycline and erythromycin in 1). Seven patients had no previous therapy of any sort. No other antibiotics were administered along with novobiocin.

Bacteriologic Findings

Gram-positive cocci (including 22 strains of hemolytic staphylococci) alone were isolated from the wounds of 20 patients and in combination with gram-negative bacteria in 5 patients. In 5 cases cultures were not obtainable. Sixteen patients had infections due to a single micro-organism, and in 9 patients 2 or more strains were isolated on culture. The bacterial strains isolated from almost all the patients in this series were tested for sensitivity in vitro to novobiocin and in many cases to other antibiotics. Strains of gram-positive bacteria were found to be very sensitive to novobiocin — that is, bacterial growth was inhibited by 6.25 microgm. per milliliter or less. All the strains of hemolytic staphylococci were resistant in vitro to penicillin and in many cases to other antibiotics (Table 2), and very sensitive to novobiocin. Of 2 penicillin-resistant strains of beta-hemolytic enterococci 1 was sensitive to novobiocin, and 1 resistant; 1 strain of alpha-hemolytic streptococcus was also very sensitive. All strains of *Ps. aeruginosa* (2), *Esch. coli* (3), *A. aerogenes* (1) and *Esch. intermedia* (2) were resistant to novobiocin.

The drug was administered orally in all cases; 1 gm. was given initially, and 1.0-1.5 gm. in divided doses per day thereafter. Most patients received 0.25 gm. every six hours. The average duration of treatment was ten days. Novobiocin was well tolerated. Of the 30 patients in this series, as well as 60 others* who received the drug, only 2 showed side effects: diarrhea in 1, and loose stools in the other. Both recovered promptly after discontinuation of therapy. No other systemic reactions were encountered in any of these patients. Renal injury was not observed. The nonprotein nitrogen was not elevated in the course of therapy. There was no evidence of hepatic injury on the basis of routine liver-function tests performed before, during and after therapy. Anemia, leukopenia, thrombopenia or agranulocytosis did not develop.

Novobiocin was rapidly absorbed from the gastrointestinal tract. After oral administration of 1.0 gm., concentrations in the blood were determined at intervals of one, two, four, and six hours by means of a colorimetric assay method.[5] The results indicated plasma concentrations of 18 to 52 microgm. per milliliter one to two hours after administration that persisted for six hours. In patients receiving 250 mg. at six-hour intervals plasma concentrations determined half an hour before the first morning dose ranged from 6 to 46 microgm. per milliliter.

Results

The results of therapy were considered good (Table 2) if there was a prompt response (within forty-eight hours), with rapid and progressive improvement. In such patients local and systemic evidence of infection subsided, drainage from the infected wounds decreased and became sterile, and the wound healed.

Results were considered poor if no such response could be demonstrated, or if the patient might be expected to have done as well without the drug, or if other measures that could have been responsible for the improvement were instituted at the same time as novobiocin therapy.

The therapeutic results were good in 28 patients and poor in 2, 1 of whom (Case 20) had extensive wound infection and slough after partial resection of irradicable carcinoma of the thyroid gland and tracheotomy. Of the various bacterial strains cultured from his wound only hemolytic *Staph. aureus* was sensitive to novobiocin. The second patient (Case 24) had a urinary-tract infection due to novobiocin-resistant bacteria and an ulcerated lesion of the toe with underlying osteomyelitis. Hemolytic *Staph. aureus* sensitive to this antibiotic was cultured from the wound. He failed to improve because of inadequate peripheral arterial circulation.

Illustrative cases of good response are as follows:

N.S., a 61-year-old man with bilateral pulmonary fibrosis, had a lobectomy for bronchiectasis. The thoracotomy wound was reopened 12 hours postoperatively to control hemorrhage from a bronchial artery. He received penicillin and streptomycin for 8 days after operation but continued to show an intermittent febrile reaction, with daily temperature elevations to 104°F. He appeared acutely ill with dyspnea, rales and rhonchi bilaterally, and a white-cell count of 21,800. A sputum culture 4 days after operation yielded hemolytic *Staph. aureus* inhibited in vitro by 0.25 microgm. of novobiocin per milliliter.

On the 8th day penicillin and streptomycin were omitted,

*These 60 patients received the antibiotic for prophylaxis or for the treatment of various medical infections. The therapeutic efficacy of the drug in these patients was not evaluated.

and novobiocin started. There was prompt defervescence, and the patient was afebrile after 48 hours of therapy. The drug was discontinued at this time because of shortness of supply. Forty-eight hours later he was again acutely ill and febrile (temperature of 103°F.). Therapy was resumed, and 12 hours later he was again afebrile and much improved. He received the drug for 5 days thereafter and remained well and asymptomatic. Sputum cultures 5 days after discontinuation of therapy showed diphtheroids and *Streptococcus viridans*.

TABLE 2. *Data in Cases of Surgical Infections Treated with Novobiocin.*

CASE NO.	DIAGNOSIS	WOUND CULTURE	IN VITRO SENSITIVITY TESTS		PREVIOUS THERAPY	DURATION OF NOVOBIOCIN THERAPY*	RESULT	
			NOVOBIOCIN	OTHER ANTIBIOTICS			BACTERIAL CULTURES	CLINICAL CONDITION OF PATIENT
						days		
1	Cellulitis & abscess of buttock	Hemolytic *Staph. aureus*	Slightly sensitive†	Resistant to penicillin & tetracyclines	Penicillin	16	No exudate	Good
2	Furunculosis	Hemolytic *Staph. aureus*	Sensitive‡	Resistant to penicillin, tetracyclines & chloramphenicol	Penicillin	19	No exudate	Good
3	Bronchopneumonia	Hemolytic *Staph. aureus*	Sensitive	Resistant to penicillin & tetracyclines	Penicillin & streptomycin	9	Diphtheroids	Good
4	Urinary-tract infection Acute pancreatitis	Hemolytic *Staph. albus* Beta-hemolytic enterococcus	Sensitive Sensitive	Resistant to penicillin	Sulfisoxazole Penicillin	6	Sterile	Good
5	Infected 3d-degree burns of back	Hemolytic *Staph. aureus* Hemolytic *Staph. albus* *Ps. fluorescens*	Sensitive Sensitive Resistant§	Resistant to penicillin	Bacitracin ointment	18	Sterile	Good
6	Osteomyelitis	Hemolytic *Staph. aureus*	Sensitive	—	Tetracycline	21	Sterile	Good
7	Cellulitis & osteomyelitis of toe Diabetes mellitus	Hemolytic *Staph. aureus* Beta-hemolytic streptococcus Beta-hemolytic enterococcus	Sensitive Sensitive Resistant	All 3 strains resistant to penicillin	None	25	Healed	Good
8	Gangrene of toe Cellulitis of foot Occlusive arteriosclerotic vascular disease Diabetes mellitus	Hemolytic *Staph. aureus* *Staph. albus* *Esch. coli*	Sensitive Sensitive Resistant	— —	None	6	No exudate	Good
9	Wound infections after colectomy	Hemolytic *Staph. aureus* Hemolytic *Staph. albus*	Sensitive Sensitive	Resistant to penicillin	Penicillin & streptomycin	4	*Ps. fluorescens*	Good
10	Wound infection after appendectomy for appendiceal peritonitis	Hemolytic *Staph. aureus*	—	—	Penicillin & streptomycin	5	No exudate, healed	Good
11	Cellulitis of chin	Hemolytic *Staph. aureus*	—	—	Penicillin & erythromycin	9	Diphtheroids	Good
12	Infected hematoma of leg Cellulitis of leg	Hemolytic *Staph. aureus*	Sensitive	Resistant to penicillin, tetracycline & erythromycin	Penicillin & tetracycline	5	Sterile	Good
13	Wound infection after closure of colostomy	Hemolytic *Staph. aureus*	Sensitive	Resistant to penicillin, streptomycin & tetracycline	Penicillin, streptomycin & chlortetracycline	8	Sterile	Good
14	Cellulitis of leg Diabetes mellitus	No exudate	—	—	None	6	—	Good
15	Furunculosis	Hemolytic *Staph. aureus*	Sensitive	Resistant to penicillin, tetracyclines, chloramphenicol & erythromycin	Penicillin, chlortetracycline & erythromycin	20	No exudate	Good

*1 gm./day.
†Bacterial growth inhibited by 12.5-25.0 microgm./ml.
‡Bacterial growth inhibited by 6.25 microgm./ml. or less.
§Bacterial growth inhibited by 50 microgm./ml. or more.

M.K., a 64-year-old woman with a past history of cholecystectomy, duodenal ulcer and hemorrhagic cystitis, was admitted to the hospital with chills, fever (maximum temperature of 103°F.) and urinary frequency. She was acute-

ly ill. There was diffuse abdominal tenderness, most marked in the epigastrium and right hypogastrium, and also acute bilateral costovertebral-angle tenderness. Urinalysis revealed 40 white cells per high-power field in the sediment. Hemolytic enterococci and *Staph. albus* were cultured from the urine. Both strains were very sensitive to novobiocin (growth inhibited by less than 0.6 microgm. per milliliter in vitro). She also had a white-cell count of 13,800 and a serum amylase of 800 units per 100 ml.

She had previously had sulfisoxazole and penicillin therapy without response. Twenty-four hours after novobiocin was first administered she was afebrile. The white-cell count was 9000. The urine became grossly clear and sterile on culture after 3 days. The blood amylase gradually regressed

TABLE 2 *(Concluded).*

CASE NO.	DIAGNOSIS	WOUND CULTURE	IN VITRO SENSITIVITY TESTS		PREVIOUS THERAPY	DURATION OF NOVOBIOCIN THERAPY*	RESULTS	
			NOVOBIOCIN	OTHER ANTIBIOTICS			BACTERIAL CULTURES	CLINICAL CONDITION OF PATIENT
						days		
16	Abscess & cellulitis of leg	Hemolytic *Staph. aureus*	Sensitive	Resistant to penicillin & tetracyclines	Penicillin	10	No exudate	Good
17	Axillary abscess Cellulitis of axilla	Hemolytic *Staph. aureus*	Sensitive	—	Penicillin Erythromycin	5	Healed	Good
18	Acute pancreatitis	—	—	—	None	4	—	Good
19	Wound infection after excision of axillary lymph node	Hemolytic *Staph. aureus*	—	—	Penicillin & streptomycin	8	Sterile	Good
20	Wound infection after thyroidectomy for thyroid carcinoma Urinary infection	Hemolytic *Staph. aureus* *Esch. intermedia* *Ps. aeruginosa*	*Staph. aureus* sensitive — all other strains resistant	Resistant to penicillin, streptomycin & tetracyclines	Penicillin, tetracycline & sulfadimetine	7	No change	Poor
	Portal cirrhosis	*Esch. intermedia* *A. aerogenes* *Ps. aeruginosa*						
21	Abscess & cellulitis of chest wall	Hemolytic *Staph. aureus*	Sensitive	—	Penicillin	11	Sterile	Good
22	Infected burns of foot	Beta-hemolytic streptococcus	Slightly sensitive	—	Bacitracin ointment locally	10	Sterile	Good
23	Wound infection after hysterectomy	Hemolytic *Staph. albus*	—	—	None	6	Sterile	Good
24	Occlusive arteriosclerotic vascular disease Ulcer & osteomyelitis of toe	Hemolytic *Staph. aureus*	Sensitive	Resistant to penicillin, tetracyclines & streptomycin	Penicillin	25	No change	Poor
	Urinary infection	*A. aerogenes* *Esch. coli*	Resistant					
25	Multiple abscesses of lower extremities	Hemolytic *Staph. albus*	Sensitive	Resistant to penicillin & tetracyclines	Penicillin	10	Sterile	Good
26	Cellulitis & lymphangitis of arm	—	—	—	Penicillin	8	—	Good
27	Abscess & cellulitis of thigh	Not obtained	—	—	None	9	Sterile	Good
28	Infected decubitus ulcer	Hemolytic *Staph. aureus*	Sensitive	Resistant to penicillin, tetracyclines & streptomycin; sensitive to bacitracin & erythromycin.	Penicillin	21	Healed	Good
29	Fistula in ano	Hemolytic *Staph. aureus* *Esch. coli*	Sensitive	Resistant to penicillin, tetracyclines & streptomycin	Penicillin & chlortetracycline	12	Healed	Good
30	Cellulitis of toe Occlusive arteriosclerotic vascular disease	No exudate	—	—	None	8	Healed	Good

*1 gm./day.
†Bacterial growth inhibited by 12.5-25.0 microgm./ml.
‡Bacterial growth inhibited by 6.25 microgm./ml. or less.
§Bacterial growth inhibited by 50 microgm./ml. or more.

to 100 units per 100 ml. in 5 days. All abdominal and flank tenderness disappeared 48 hours after novobiocin therapy was instituted.

C.W., a 79-year-old woman with diabetes, was admitted to the hospital with a 12-hour history of swelling, redness and pain of the left foot and lower leg extending to the knee. There was a small crack in the skin over the medial malleolus. The lower leg was erythematous, tender, hot and swollen. She had a temperature of 101°F. and a white-cell count of 12,000. No culture was obtained. On bed rest, novobiocin therapy and regulation of the diabetes she responded within 24 hours. The edema and cellulitis subsided rapidly. The temperature became normal, and she was discharged well 6 days later.

D.R., a 57-year-old man, had an anterior resection of the sigmoid for carcinoma. Postoperatively he received penicillin and streptomycin. He was febrile from the 2d day, with daily temperature elevations of 101-102°F. and a white-cell count of 19,000-25,000. On the 14th day penicillin and streptomycin were discontinued and replaced by novobiocin. At this time small amounts of pus were draining from the abdominal wound. Hemolytic *Staph. aureus* and *Staph. albus* were obtained on culture. The former was inhibited in vitro by 0.1 microgm. of novobiocin per milliliter. He was afebrile within 24 hours, and shortly thereafter the discharge from the abdominal wound was sterile on culture. Therapy was discontinued after 5 days. Convalescence thereafter was uneventful.

F.V., a 55-year-old diabetic woman, had incision and drainage of an abscess of the buttocks. The culture revealed *Staph. albus*. The wound was packed, and she received penicillin. Nineteen days later there were still signs of infection, with tenderness, redness and induration of the buttocks and continued drainage from the abscess cavity, from which hemolytic *Staph. aureus* sensitive to novobiocin (growth inhibited by 0.25 microgm. per milliliter) was cultured. Penicillin was discontinued, and novobiocin started. The wound rapidly showed improvement. Drainage decreased and became sterile. Therapy was discontinued after 16 days, when the wound was healed.

Discussion

Novobiocin represents an addition to the antibiotic armamentarium. These preliminary results indicate its efficacy against strains of staphylococci and certain other gram-positive bacteria resistant to other antibiotics.

The drug administered orally was rapidly absorbed, yielding blood levels that appeared adequate for inhibition of bacterial growth. It was not possible to evaluate the results of in vitro sensitivity tests in terms of the possible clinical effectiveness of the drug because of inadequate number of patients in whom these two considerations could be correlated. However, since plasma concentrations achieved with the usual daily oral doses generally range from 6 to 46 microgm. per milliliter bacterial strains inhibited in vitro by 12.5 microgm. or less can probably be controlled in patients by this drug.

Summary

Novobiocin (Cathomycin) was extremely effective against strains of gram-positive bacteria in vitro, including those found to be resistant to penicillin, the tetracyclines and erythromycin.

Patients with a variety of surgical infections due largely to strains of hemolytic staphylococci responded to the drug, which was effective in the treatment of infections that had failed to respond to other antibiotics.

After oral administration of 0.25 gm. every six hours novobiocin was absorbed rapidly, and plasma concentrations ranged from 6 to 46 microgm. per milliliter.

The drug was well tolerated. Only 2 of 90 patients had mild gastrointestinal side effects. There were no other systemic reactions.

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SPECIAL ARTICLE

CHEMICAL CONTROL OF PULMONARY VENTILATION*

III. The "Reaction Theory" of Respiratory Control

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FIFTY-FIVE years ago, while a student, I wrote my first scientific paper.[1] Its subject was the effect of carbon dioxide on the central nervous system. My research showed that carbon dioxide has two opposing but simultaneous effects, excitatory and inhibitory. As a logical postulate it seemed to me impossible that these two effects could be referred to the same substance. At that time I did not succeed in solving the problem. It was only ten years later that I found the answer to the apparent contradiction. I had discovered a method by which newborn mammals could be kept alive for some time by perfusion with oxygen-saturated salt solution at room temperature.[2] In these experiments I noticed that the little animals showed lively reflex movements to different stimuli — for example, pinching — but no automatic respiratory movements. They were in a state of permanent apnea. But if 2 or 3 per cent carbon dioxide was added to the solution, corresponding at room temperature approximately to blood carbon dioxide tension, the normal regular breathing movements started. It is known, of course, that carbon dioxide exists in water in two forms: as the dissolved gas and in combination with water as carbonic acid, although present only to the small extent of less than 1 per cent. This acid for its part is mostly dissociated into the bicarbonate radical and hydrogen ion. Its effect, like that of acids in general, depends on the resulting cH. It therefore occurred to me that other acids might have the same effect on respiration, and I found my idea confirmed. Addition of such acids — for example, one-thousandth normal hydrochloric acid — produced the same regular rhythmic respiratory movements. Accordingly, it seemed to me that my logical postulate was correct: it was not the same substance exercising two opposing effects but, on the one hand the dissolved carbon dioxide, which my earlier researches had shown to have a specific narcotic effect in higher concentrations, and on the other hand the unspecific excitatory effect of the hydrogen ion of dissociated acids — in this case, carbonic acid.

It is a natural tendency in science to look for a common cause behind similar effects. In the physiology of respiration, too, there has been a long-standing search for a common basis for the hyperpnea produced by excess of carbon dioxide and the extremely similar hyperpnea produced by lack of oxygen. A great many people even up to the present time believed this common factor to be carbon dioxide. But in many cases the increases in ventilation by no means parallel the carbon dioxide tension. Sometimes, indeed, they diverge in opposite directions, which is exactly what happens during oxygen lack. Some investigators sought to explain this objection by postulating an increase in general excitability of the respiratory center under the influence of oxygen lack, so that lower carbon dioxide tensions have a greater effect. In my second lecture I sought to prove that this is no explanation at all. The expression "increase of excitability" is nothing more than another method of describing the observed fact without making it any more understandable.

REACTION THEORY

The proof that the effect of carbon dioxide is in reality an effect of the hydrogen ions that it produces, seemed to me to open the possibility of providing a unified explanation of the two forms of hyperpnea. I believed that I had found the common origin to be the blood pH, when I considered the well established fact that insufficient oxygen supply leads to the production of acid substances in different organs, especially the central nervous system. So I presented the theory that neither carbon dioxide pressure nor oxygen lack was directly responsible for the control of respiration, but only the blood pH. This was the first formulation of the theory to which I later gave the designation "reaction theory."[3]

As I explained in my previous lecture we are indebted to Lawrence Henderson for setting forth the acid-base equilibrium of the blood as represented in the Henderson equation. As can easily be seen, the cH is proportional to the concentration and so to the pressure of carbon dioxide. It therefore appeared to Henderson difficult to decide whether the cH or carbon dioxide is the effective factor in respiratory control. I found quite a simple method of doing this. If an acid is injected into the blood stream the cH and carbon dioxide pressure do not change in the same but in the opposite direction. Under these conditions it can be seen that pulmonary ventilation parallels the cH — that is, it opposes the carbon dioxide pressure.

Thus, the first part of the reaction theory was remarkably well confirmed, in spite of some objections,

*The third Edward K. Dunham Lecture, delivered at Harvard Medical School, Boston, October 19, 1955.

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which are discussed below. However, as far as the second part about oxygen lack is concerned, I was the first to recognize that it was erroneous as presented in its first formulation. When I investigated the blood pH during oxygen lack I found it to be shifted — not as I expected toward the acid side but in fact toward the alkaline side. But the explanation seemed simple. The central nervous system is the organ of the body that, more than any other, is sensitive to oxygen lack, so that here, first of all, an accumulation of acids should occur, exciting the respiratory center. The following hyperpnea, produced centrogenically, must have the secondary effect of washing out the carbon dioxide and thus shifting the reaction to the alkaline side.

So the second formulation of the reaction theory followed. The chemical control of respiration can be achieved in two ways, either *hematogenically* by a change in pH of the blood, when this is the primarily occurring factor, or *centrogenically* by a change of pH in the center itself, when this is primary, as during oxygen lack. But a production of acids in centers with normal blood supply had not been experimentally demonstrated. And when, ten years later, the discovery of the chemoreceptors showed that it was their excitatory action that caused the hypoxic increase of respiration, it seemed that there was no longer any foundation for the second part of the reaction theory. However, before the discoveries that have reinstated this second part of the theory are mentioned, the criticisms that have been brought against the first part should be discussed. The partisans of the carbon dioxide theory attempted to prove that a specific action of this gas on the respiratory center and not the change of pH was responsible for exciting the reaction. And this opinion is still held by a number of research workers.

The most important objection is the behavior of bicarbonate, discovered by Collip,[4] which is even now cited in many textbooks as a proof against the reaction theory. If bicarbonate is injected into the blood stream, an *increase* of ventilation is often seen, at least at first, although the blood pH is shifted to the alkaline and not to the acid side. The solution of this problem is due to ingenious experiments by Jacobs[5,5a] in Philadelphia. They are so fundamental to an understanding of the whole question of the chemical control of respiration that they must be treated in greater detail. In 1920 Jacobs observed that saturated solutions of carbon dioxide were much more poisonous for tadpoles and protozoa than other solutions of organic acids with the same pH. This poisonous effect continued even when the pH had been brought to neutrality by the addition of bicarbonate. He sought to explain this by the great diffusibility of undissociated carbonic acid. This would also explain why the taste of an alkaline mixture of bicarbonate and carbon dioxide is acid although it is generally acknowledged that acid taste depends on pH. Jacobs also pointed out that this fact applied to the respiratory center could remove the contradictions about respiratory control.[5] He showed that the same principle was valid in flowers, whose color change was identical in a bicarbonate solution saturated with carbon dioxide and in a pure carbon dioxide solution, although the cH of the latter was four thousand times greater than that of the former.

In an especially interesting way Jacobs was able to show the independence of the reaction in the interior of cells from the reaction of their surroundings. He put sea-urchin eggs colored pink with neutral red in three solutions, each having a pH of approximately 7.2. The first solution was half-molar sodium chloride with a trace of sodium bicarbonate, the second half-molar sodium bicarbonate saturated with carbon dioxide, and the third half-molar ammonium chloride with a little ammonium hydroxide. In the first solution the color of the eggs remained unchanged; in the second they showed an acid reaction, and in the third an alkaline reaction. I was able to duplicate this phenomenon, which Jacobs had demonstrated on living material, on nonliving membranes. If solutions containing carbon dioxide and bicarbonate are separated by a collodion membrane they achieve the same pH on both sides because the membrane is permeable to the undissociated molecules as well as to the ions in question. But if the collodion membrane is changed to a lipoid membrane by oiling, the membrane is no longer permeable to ions, and by the diffusion of carbonic acid it is possible to produce an acid solution alongside an alkaline bicarbonate solution. The physicochemical process is obviously as follows: In the original solution the equation $CO_3^- \rightleftharpoons CO_2 + OH^-$ gives the solution its alkaline properties. The carbon dioxide wanders through the membrane to the other side, where it becomes $CO_2 + H_2O \rightleftharpoons HCO_3^- + H^+$, thus giving an acid reaction.

Here is, indeed, a specific effect of carbon dioxide but one that is not due to any specific structural property of the carbon dioxide molecule; it is due to the fact that its great diffusibility permits the exercise of its unspecific effect as an acid in places that are inaccessible to other acids. Perhaps the most striking experiment proving this was performed in Hess's[6] laboratory in Zürich. The vein of a frog was drawn over the antimony electrode of an apparatus for measuring pH and was dipped into solutions of different pH. The antimony electrode immediately showed the pH change when carbon dioxide was present in the solution, and not at all with other acid solutions without carbon dioxide. Even a change of pH from 7.5 to 3.2 remained without effect for several minutes. Here, when any specific molecular effect of the carbon dioxide is obviously excluded, it is clear that its apparently specific effect is nothing but the nonspecific action that an acid can exercise on account of its great specific diffusibility.

Gesell and Hertzman,[7,7a] in Ann Arbor, thirty years

ago, first tried to measure directly the pH of fluids inside the body. They found that intravenous injection of bicarbonate produces a shift of pH of the arterial blood and to a lesser degree of the venous blood to the alkaline side. But this was accompanied by the opposite effect—namely, a shift to the acid side in the cerebrospinal fluid. This is an excellent repetition of Jacobs's experiment, applied to mammals. The membrane of the sea-urchin egg is replaced by the so-called barrier between blood and cerebrospinal fluid. Evidently, the effect on the respiratory center depends on the pH of the latter as well as on the blood pH. Thus, the objection stated above — namely, the excitatory effect of alkaline bicarbonate solutions on lung ventilation — is cleared up entirely in accordance with the reaction theory.

There is still another serious objection against the theory, an inverted counterpart of the effect of bicarbonate — that is, the respiratory effect of ammonium chloride. It is an established fact that incorporation of this substance produces a strong shift of the blood pH to the acid side. But Nielsen found that the increase of respiration produced by ammonium chloride acidosis was much less than that produced by breathing of air containing carbon dioxide for several days. On the contrary the change of pH in the latter case was incomparably smaller. Nielsen[8] therefore concluded that the carbon dioxide must have a specific effect on respiration.

To clear up this situation the phenomenon of ammonium chloride acidosis has been thoroughly investigated.[9,10] According to J. B. S. Haldane, who was the first to study the matter in detail, the acidosis is due to the fact that the ammonia part of ammonium chloride taken by mouth was retained in the liver to form urea. The remaining hydrochloric acid was released and produced acidosis. This theory is still quite commonly accepted. It was first of all established that this theory is incorrect.[9,10] Ammonium chloride produces acidosis in dogs not only when given by mouth but also when intravenously injected. This alone makes the urea theory very improbable, because in this way ammonium chloride does not go directly to the liver, and it is known that the urea formation is greatly reduced when the liver is bypassed by an Eck fistula. But even the complete isolation of the liver from the circulation does not prevent the production of acidosis.

A simple procedure illustrated this point. The blood of the hepatic portal vein was directly led to one of the jugular veins, and all vessels entering and leaving the liver were closed off by a common ligature. The completeness of this isolation of the liver from all blood supply was shown by the fact that an incision produced no bleeding. In spite of this, ammonium chloride injection led to an acidosis that shifted the blood pH by 0.1 to 0.2 to the acid side. And now, with the effects with bicarbonate in mind, the pH of the blood and of the cerebrospinal fluid was investigated. It was found, in fact, that the conditions reflected Jacobs's experiments: whereas the blood pH was strongly shifted to the acid side the cerebrospinal fluid became more alkaline. The increase of ventilation observed in ammonium chloride acidosis is clearly the algebraic sum of the excitatory effect of the increase of the cH of the blood and the inhibitory effect of the decrease of the cH of the spinal fluid. This is just the opposite of the conditions found by Gesell with bicarbonate. In Gesell's experiment the undissociated carbon dioxide produced by the dissociation of the bicarbonate ion diffuses through the barrier and causes acidity on the other side. In exactly the same way the undissociated ammonia appearing from the dissociation of the ammonium ion, as in the equation $NH_4^+ \rightleftharpoons NH_3 + H^+$, passes through the barrier between blood and cerebrospinal fluid, which is impermeable to ions. On the other side of the barrier the ammonia again ionizes according to the equation $NH_3 + H_2O \rightleftharpoons NH_4^+ + OH^-$, thus causing alkalinity. With bicarbonate, in spite of the shift of blood pH to the alkaline side, respiration may be increased because the reaction of the cerebrospinal fluid has shifted to the acid side. Similarly, with ammonium chloride, the increase of respiration is not as great as the strong shift of the blood pH to the acid side demands, because the alkaline reaction of the cerebrospinal fluid works in the sense of diminution of ventilation. Here, too, there is a complete agreement with the reaction theory.

Reaction Theory and Hypoxia

To return to the problem of oxygen lack, after it was established that hypoxia exerted its excitatory effect exclusively through the glomera and the chemoreceptors and that after removal of these structures hypoxia had even a reducing effect on respiration, all relation between the effect of oxygen lack and hydrogen-ion concentration seemed nonexistent. But, in 1939, Euler, Liljestrand and Zotterman,[11] using the action potentials of the carotid nerve, investigated whether excitation due to oxygen lack and that due to carbon dioxide are carried by the same chemoreceptor fibers. They found a complete similarity in the reduction of these action potentials, when the number of active chemoreceptor fibers was diminished by cutting till only a few remained. Still more important was the observation that a small quantity of alkali temporarily stopped the action potentials completely, whether produced by oxygen lack or by carbon dioxide.

These experiments are a clear proof that the same chemoreceptor fibers and the same excitatory mechanism are operative in reflex respiration control in hypoxia as in carbon dioxide excess. Since this mechanism is put out of action by a shift to the alkaline side the only possibility is that its excitation is due

to an increase of cH. And so the reaction theory, but in a new form, was extended again to include hypoxia. Whereas in its previous edition the effects of oxygen lack were explained by centrogenic acidity, now *glomerogenic* acidity must be substituted.

But how is this acidity generated in the glomera? For carbon dioxide the answer is given immediately by its own dissociation. In the equation $CO_2 + H_2O \rightleftharpoons H_2CO_3 \rightleftharpoons HCO_3^- + H^+$ the latter part is an ionic reaction that is virtually instantaneous. But the first part is molecular and needs time. As with all molecular reactions in the organism that need to be speeded up, a specific enzyme, carbonic anhydrase, has been evolved, which is formed wherever rapid dissociation of carbonic acid is demanded. Indeed, in the glomus, it is present in large quantities, proving that it is the dissociated acid and not the metabolic carbon dioxide that is effective.

As far as oxygen lack is concerned, the same considerations as made for the centers must be applied to the glomera. How is it possible that a chemical substance can be effective on account of its absence? Evidently, it must occur because some metabolic products are manufactured in this absence. The acidic metabolic materials suggested for the centers may well be produced in the glomera. So every decrease in oxygen tension would lead to an increase, and every rise in oxygen tension to a decrease of cH in the glomera, with corresponding effects on pulmonary ventilation.

Thus, the excitation in the glomera occurs in two ways: *exoglomerogenically,* through the blood pH, and *endoglomerogenically,* through the production of hydrogen ions in the glomus itself, depending on the oxygen pressure. This was the third formulation of the reaction theory. But this was also not sufficient to explain all the observed phenomena.

Effect of Chemoreceptors in the Reaction Theory

Mrs. Gökhan and I came across a most striking fact during our investigations of ammonium chloride acidosis to find out how dogs fed that compound behaved when their chemoreceptors had been removed. We found the shifts of pH to be the same as that in normal dogs — namely, to the acid side in the blood and to the alkaline side in the cerebrospinal fluid. But the effect on lung ventilation was quite different: not only was the slight increase to be observed in normal dogs missing, but also, in its place, there was a considerable reduction of the respiratory volume *below* the normal level.

Table 1, based on an experiment in which ammonium chloride was fed to the same dog twice before and twice after operative removal of the sinus chemoreceptors, shows that the direction of pH shift was not changed by the operation. But the lung ventilation was greatly reduced after the denervation of the sinus chemoreceptors, in contrast to the weak increase before it. Since the decrease of the cH of the blood after removal of chemoreceptors is incapable of any effect one is driven to the surprising conclusion that the blood pH acts on the center not directly but only through the chemoreceptors.

But in the first lecture it was pointed out that carbon dioxide exerts its effect not only by way of the chemoreceptors but also and even predominantly by a direct action on the centers, as attested by the fact that its effect is still present to a great extent after removal of the chemoreceptors.

Chemoreceptor Stimulants and Blood-Brain Barrier

To explain this apparent paradox one must consider a group of chemical substances that I have classed together as *chemoreceptor stimulants.* Heymans and Bouckaert[12] discovered that a group of substances, whose excitatory action on respiration was already known, acted almost exclusively by way of chemoreceptor reflexes; if they reached the centers by way of the blood stream they were either ineffective or effective only in enormously increased doses. These authors demonstrated this by an ingenious experimental arrangement (Fig. 1).

On one side of the dog's head all the vessels except the carotid sinus were ligated, but at the same time both the blood supply to the sinus itself and its innervation were carefully preserved. On the other side, however, the internal carotid and the occipital arteries were left open, but the sinus region was completely denervated. Thus, the center can be affected on the right side only through the carotid nerve and on the left side only by the blood stream. If a small quantity of such stimulating substances as sodium sulfide and lobeline is injected into the common carotid of the right side (the side with intact chemoreceptors) a strong hyperpnea is produced. This can only be the result of reflex action. If the injection is made on the other side, so that the substance flows unhindered through the denervated sinus to the centers, no effect is observed.

It was pointed out, in the consideration of ammonium chloride acidosis, that the change of cH affected respiration only as long as chemoreceptor reflexes were possible and no longer occurred after removal of the chemoreceptors. This seemed to be entirely analogous to the effects of chemoreceptor stimulants just mentioned. It was demonstrated that it is the barrier between blood and cerebrospinal fluid that prevents the decrease of blood pH from spreading to the cerebrospinal fluid and the brain. This led us to the idea that it might be the barrier that was also preventing chemoreceptor stimulants from being effective after denervation, because these substances cannot pass the barrier. If this supposition is correct, these substances should regain their effectiveness if they are directly introduced into the cerebrospinal

fluid, thus avoiding the barrier. Our experiments have proved that this is indeed so.

We conducted our experiments on dogs whose sinus nerves had been severed. (I should like to mention that in all cases we restricted ourselves to the sinus chemoreceptors; the aortic chemoreceptors, which are of small importance for respiratory control, appear to play no part at all in this connection.) The first substance investigated, again, was ammonium chloride. The intravenous injection of a small quantity either had no effect at all or, as mentioned, caused a reduction in respiratory volume — in 1 case, for example, of 33 per cent. Half this dose was infactor in the control of lung ventilation. The role of this barrier explains a phenomenon that has often been observed and interpreted in a variety of erroneous ways. The phenomenon consists of the time difference between carbon dioxide and cH acting glomerogenically and centrogenically. In the first case the effect is nearly immediate whereas in the second a considerable time elapses between increase of carbon dioxide tension or cH in the blood and the increase of ventilation. In the first case the blood is in direct contact with the sensitive end organs of the chemoreceptors whereas in the second physicochemical processes at the barrier are interposed.

TABLE 1. *Ammonium Chloride Acidosis.*

	DATE	EXPERIMENTAL CONDITION	BLOOD pH	CEREBROSPINAL-FLUID pH	RESPIRATORY VOLUME
					ml./min.
Normal animal:					
	Oct. 4	Normal	7.36	7.28	5750
	Oct. 9	After 5 days of ammonium chloride	7.28 (−0.08)	7.34 (+0.06)	6000 (+250)
	Oct. 24	Normal	7.42	7.34	6000
	Oct. 31	After 6 days of ammonium chloride	7.24 (−0.18)	7.37 (+0.03)	6250 (+250)
Left sinus chemoreceptors removed & right sinus chemoreceptors denervated (on Nov. 5):					
	Nov. 14	Normal	7.32	7.12	4500
	Nov. 22	After 5 days of ammonium chloride	7.22 (−0.10)	7.24 (+0.12)	3650 (−850)
	Dec. 5	Normal	7.31	7.14	4500
	Dec. 18	Normal	—	—	6000
	Dec. 24	After 7 days of ammonium chloride	7.26 (−0.05)	7.31 (+0.17)	4600 (−1400)
	Jan. 4	Normal	—	—	5000

jected suboccipitally into the fourth ventricle, and now ventilation increased by 80 per cent. The same effect was obtained with the well known respiratory stimulant, lobeline, and with sodium cyanide. From these results it is clear that the chemoreceptor stimulants are substances that under normal conditions are effective only by way of chemoreceptor reflexes because they are unable to pass the barrier between blood and cerebrospinal fluid. But the hydrogen ion, which is a stimulant of this kind, is also unable to cross this barrier and so behaves in exactly the same way as in Hess's experiments, in which a length of frog's vein drawn over the electrode of a pH meter was the equivalent of the barrier. It is only undissociated carbon dioxide that can pass through the barriers and on the other side produce by dissociation the hydrogen ions responsible for the effect. Accordingly, the hydrogen ions can be effective in two ways: by exciting the glomus mechanism to reflex activity and by passing through the ion-impermeable barrier in the form of undissociated carbon dioxide and affecting the centers directly by means of the hydrogen ions produced there.

Thus, the blood-brain barrier, which until now has received no consideration in the physiology of respiration, is an important and sometimes even decisive

The difference between peripheral and central effects has given rise to a problem that has led to several discussions in recent times. It started with the observation by Comroe and Schmidt[13] that the respiratory centers apparently lose their sensitivity to carbon dioxide during very deep anesthesia so that respiration is only maintained by the chemoreceptors. If these are put out of action, either by cutting or even by high oxygen pressure only, respiration stops. The chemoreceptors are, in their words, the "ultimum moriens"—the last resort of the respiratory mechanism. Similar observations were later made by a number of different authors. Beecher and Moyer[14] report experiments with anesthetized dogs whose respiration could only be maintained by slight hypoxia, stopping as soon as pure oxygen was administered.

Garcia Banus and his collaborators[15] were the first who, relying on such observations, suggested a hypothesis that at first sight seemed strange. They proposed two different systems in the respiratory center, the one sensitive to the pH in the interior of the cells themselves and the other sensitive to the incoming reflex impulses. The first could be put out of action by anesthesia, the second, however, being more resistant. The Swedish worker Åström[16] has gone so far as to postulate two entirely different centers, — a "respira-

tory chemocenter" and a "respiratory reflex center," — only the first of which is affected by anesthesia.

In new experiments Euler and Söderberg[17] came to a slightly different hypothesis. Their experiments were conducted on curarized decerebrate cats, from the central stumps of the severed phrenic nerves of which action potentials were led off. These represented, of course, the motor respiratory impulses. The stimulation of different peripheral nerves as well as breathing of 6.5 per cent carbon dioxide produced an increase of these action potentials. If these animals were anesthetized with chloralose the action potentials produced by carbon dioxide were greatly reduced whereas those resulting from reflex stimulation remained as before. It appeared improbable that the same cells producing the motor impulses could be affected by anesthesia through carbon dioxide but not through reflex impulses. Consequently, the authors postulated the existence of special intracentral chemoreceptors sensitive to carbon dioxide that were put out of action by anesthesia. I do not feel persuaded that this conclusion is correct. It is remarkable that none of the authors mentioned above have taken into account the fact that carbon dioxide has not only a central effect but also a peripheral one on the chemoreceptors. Therefore, the problem is not why the centers have lost their sensitivity to carbon dioxide during deep anesthesia but not their sensitivity to reflex impulses: the real problem is that of the question how, during deep anesthesia, the sensitivity to carbon dioxide is frequently lost both centrally and peripherally. This has not yet been investigated in detail. But it seems to me that the reason lies in the anesthetic effect of the carbon dioxide itself, added to that of the anesthetizing agent. That this gas in high concentration has a paralyzing effect is well known. As mentioned at the beginning it was the observation that carbon dioxide had simultaneously both an augmenting and a diminishing effect on excitation that led me to the conclusion that these two opposite effects depended on two separate mechanisms and hence to the formulation of the reaction theory. It has recently been shown that, in man, breathing of 5 per cent carbon dioxide reduces the corneal reflex and, astonishingly enough, that a concentration as low as 0.1 per cent has a diminishing effect on the excitability of peripheral nerves. It therefore seems not at all improbable that the supplementing of deep anesthesia by such a paralyzing factor increases its effect. For this reason it cannot be used as an argument for the existence of chemically sensitive receptors in the centers.

However, the experiments made by Mrs. Gökhan and me on chemoreceptor stimulants seem indeed to point in this direction. The fact that these materials cause stimulation in the glomus mechanism and not in other peripheral end organs suggests that a specific type of end organ is needed for excitation. But most striking is the effect of cyanides, which also belong to the class of chemoreceptor stimulants. It is universally accepted that the effect of cyanides depends

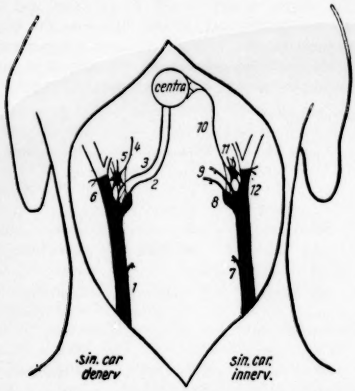
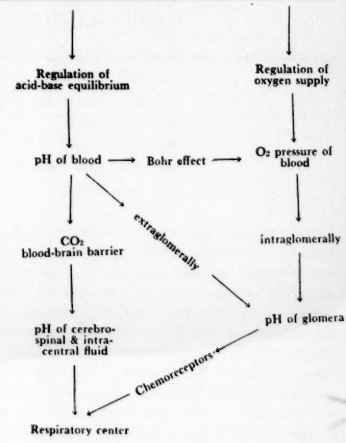


FIGURE 1. *Comparison of Centrogenic and Chemoreflex Control of Respiration (after Heymans and Bouckaert[12]). 1—carotis communis. 2—carotis interna. 3—occipital artery. 4—right carotid-sinus nerve severed. 5—glomus caroticum. 6—right external carotid ligated. 7—left common carotid. 8—left carotid sinus with the internal carotid ligated. 9—occipital artery ligated. 10—left carotid-sinus nerve intact. 11—left glomus caroticum. 12—left external carotid ligated.*

TABLE 2. *Scheme of the "Reaction Theory" of Respiratory Control.*



on the inhibition of oxidative processes. In this way their effect should be similar to that of lack of oxygen. But lack of oxygen leads not to an increase but rather to a decrease of respiration, if the chemoreceptors have been removed. Therefore, one might have expected the same effect when cyanide was directly introduced into the cerebrospinal fluid. Instead, there is an excitation, and this indeed might be used as an argument for the existence of special chemoreceptive units in the centers themselves.

Last Formulation of the "Reaction Theory"

If this still problematic question is put aside a fourth formulation of the reaction theory may be advanced. The task of pulmonary ventilation is, as emphasized above several times, a twofold one: maintaining the equilibrium between oxygen demand and oxygen supply; and maintaining the acid-base equilibrium.

The way in which lung ventilation is controlled for the purpose, on the one hand, of regulating the pH and, on the other, of regulating oxygen equilibrium, is shown diagrammatically in Table 2.

If the acid-base equilibrium is upset hematogenically — for example, by breathing of carbon dioxide or by acid metabolic products — the change of pH acts through three channels: through the Bohr effect, which changes the oxygen pressure in the same sense as the cH; extraglomerogenically, through an effect on the pH of the glomus cells, produced by the change of pH of the blood bathing them; and most important of all, through its effect on the H_2CO_3: HCO_3^- ratio at the barrier between blood and cerebrospinal fluid. It is this ratio that determines the reaction of the fluids bathing the centers themselves, and thus the pH of the motor cells that emit the respiratory impulses.

Disturbances of oxygen pressure are also regulated by way of lung ventilation. This comes about intraglomerogenically, in the sense that metabolic processes in the glomus cells themselves, depending on the oxygen pressure, determine the pH of these structures, and thus the magnitude of the chemoreceptor drive.

Conclusions

I have come to the end of the task I set myself. I have attempted to reduce to a single basis the various ways of chemical control of respiration that can be observed — namely, the cH in the responsible structures. It seems to me that there is no known phenomenon that opposes this last formulation of the "reaction theory" or cannot be explained by it. But I shall never forget the words of Jules Thomson: "A scientific idea is a tool and not a creed."

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MEDICAL PROGRESS

MANAGEMENT OF PYELONEPHRITIS*

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RECENT advances in knowledge and understanding of the nature and functional disturbances of pyelonephritis have led to more rational therapy. The purpose of this communication is to review this progress.

Pyelonephritis, the commonest of all renal diseases, is due to bacterial infection of the kidney. In infections of the urinary tract, the kidney must always be assumed to be involved until proved otherwise, since

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there is often no reliable method of differentiating infection of the lower and upper urinary tract. However, urethral, prostatic and rarely bladder infections may occur without renal involvement.

Pathogenesis

Recently, Beeson[1] has brought together and appraised many of the clinical observations and experimental data that bear on the pathogenesis of pyelonephritis. His excellent, scholarly presentation should be read by students of the disease. Hayman's[2] brief paper, which deals with the problems that pertain to the pathogenesis of pyelonephritis, is also recommended.

Bacteriologic Considerations

Bacteriology of the normal urinary tract. The presence of a wide variety of bacteria within the urethra of normal persons has been reported by many observers. In males, diphtheroids, avirulent staphylococci, *Streptococcus faecalis, Escherichia coli, Str. viridans* and bacilli of the *Proteus vulgaris* group have been found as the chief inhabitants whereas in 10 to 16 per cent of adult females *Esch. coli* was cultured.[3,4] It is obvious that bacteria normally resident in the urethra may contaminate urine spontaneously voided or collected by a catheter.

The reports on cultures of bladder and ureteral urine from "normal" subjects may be difficult to evaluate because bacteria may be found in abundance, without pyuria, in chronic asymptomatic pyelonephritis.[5] Furthermore, one cannot eliminate the possibility of false-positive results due to contamination by bacteria introduced into the bladder urine during passage of the catheter or cystoscope. However, bacterial counts may be of considerable assistance in differentiating significant bacteriuria and contaminants.[6-8]

Source of bacteria infecting the urinary tract. The source of the bacteria that cause pyelonephritis is in the flora of the intestinal tract since coliform bacilli are responsible for most of the early uncomplicated cases, and enterococci, proteus and pseudomonas are found in complicated cases of long standing.[1]

Possible routes by which bacteria reach the kidney. The pathways by which infection is conveyed have been the subject of controversy for decades. Infection of the kidney may occur through the lymphatics; the blood stream; ascending pathway via the ureter; and direct extension of an infectious process.

Infection by way of the lymphatics. Lymphatic connections between the appendix and cecum and the right kidney may explain the greater frequency of right-sided pyelonephritis. It is noteworthy that lymphatic connection between the colon and the left kidney has not been found. Spread of infection from the lower to the upper urinary tract via the lymphatics appears unlikely on anatomic grounds.[9] The lymphatics probably play an important part in the spread of infection within the kidney. An intricate intercommunicating network exists in the cortex and medulla, which communicate with the lymphatics of the pelvis and with those of the capsule.

Hematogenous infection. Metastatic coccal infections of the kidney develop as a result of dissemination through the blood stream from a primary focus, such as a carbuncle. How and under what conditions bacteria from the intestinal tract enter the blood stream and invade the kidney are not known. Microorganisms may reach the blood stream after instrumentation of the urethra.[10] In the absence of instrumentation, bacteria may sometimes reach the kidney during the course of a lower-urinary-tract infection as a result of normal lymphatic drainage from the bladder into the thoracic duct and blood stream. The site of the earliest lesions in hematogenous and ascending infection may be in the renal cortex, in the region of the convoluted tubules or in the central portion of the papillae. These facts emphasize the difficulty of deciding from a pathologic standpoint whether the infection is hematogenous or ascending in origin.[11]

Ascending infection. Most authors agree that bacteria — chiefly fecal flora — may enter the bladder after contamination of the urethra. The greater incidence of urinary-tract infection in female children is explained on this basis. Bacteria migrate out of the bladder into the ureters and from there to the kidneys as a result of vesicoureteral or ureteral reflux. Vesicoureteral reflux may be the consequence of inflammatory changes in the intravesical portion of the ureter, with conversion of the lower end of the normally, easily compressible ureter into a rigid or semirigid tube. Furthermore, obstruction of the lower urinary tract due to contracture of the vesical outlet, prostatic hypertrophy, congenital valves of the posterior urethra, urethral stricture or spastic neuromuscular disease may cause sufficient intracystic back pressure to injure or destroy the mechanism of the ureterovesical valve; secondary infection may aggravate or accelerate the ureterovesical-valve injury.[3] Ultimately, vesical contraction directly forces infected urine in the bladder up the ureter. Ureterovesical reflux has been demonstrated by the technic of the "delayed cystogram."[12,13]

Direct extension of an infectious process. Renal involvement by direct extension from adjacent infection is rare. However, lower-urinary-tract infection may result from perforation of the bladder by diverticulitis of the sigmoid or from pelvic inflammatory disease. Infection of the kidney may develop subsequently.

Although in some cases the clinical history, symptomatology and urologic findings may suggest the route of bacterial invasion of the kidney, in most cases this cannot be established. Furthermore, it is possible that bacteria invade the kidney by more than one route.

Bacteriology of pyelonephritis. The direct cause of pyelonephritis is bacterial invasion of the kidney. The

most common bacteria found in acute and chronic pyelonephritis are *Esch. coli* and closely related bacteria. However, the frequency of staphylococci, enterococci and members of the genera proteus, aerobacter and pseudomonas increases in chronic and obstructive pyelonephritis and especially in the cases that have followed catheterization, instrumentation or antecedent antibacterial therapy. The incidence of various bacterial species in a given series of cases reflects the type of pyelonephritis and the previous treatment of the patients involved.[6] Furthermore, single bacterial species are found in the urine in 80 to 100 per cent of cases of acute uncomplicated pyelonephritis whereas in pyelonephritis complicated by structural abnormalities of the urinary tract the incidence of pure cultures may be as low as 20 per cent.[14]

It should be emphasized that cases of symptomatic pyelonephritis may be seen in which bacteria cannot be found either in the urinary sediment or on culture for long periods in the absence of demonstrable obstruction. A diagnosis of tuberculosis is usually suspected. Furthermore, in cases of advanced pyelonephritis accompanied by marked cicatricial changes or impaired renal function, abacterial pyuria may also be observed.

Host Susceptibility and Resistance to Infection

The factors that predispose to pyelonephritis are quite diverse and often can be identified. They are as follows: age of the patient; sex of the patient; mechanical factors; iatrogenic implantation of bacteria in the urinary tract; diabetes mellitus; and others.

Age of the patient. Weiss and Parker,[15] on the basis of autopsied material, found that pyelonephritis was common in early childhood, in pregnancy and again in old age. In infancy and childhood congenital malformations of the kidney and of the urinary tract predispose to the disease. Pyelonephritis in children under three years of age during the diaper period when fecal contamination around and in the urethra is likely to occur is probably due to ascending urinary-tract infection.

Sex of the patient. In childhood pyelonephritis is commoner in females than in males. This has been attributed to an ascending urinary-tract infection that follows fecal contamination of the short urethra of the female child. "Honeymoon cystitis and pyelitis" may be precipitated in women by sexual intercourse during the first month of marriage. The pathogenesis of this disorder is unknown.

Pregnancy may predispose to pyelonephritis. Dilatation of the kidney pelves and ureters, more marked on the right side, appears in most cases after the third month of pregnancy and usually disappears several weeks post partum. The involvement of the ureters extends only to the pelvic brim. In spite of the fact that ureteral dilatation is so commonly seen as a result of atony and obstruction by the gravid uterus, pyelonephritis occurs only in about 2 per cent of pregnant women. The source and pathway of infection to the kidney are unknown. It is obvious that the pathogenesis of pyelonephritis of pregnancy remains to be clarified.

In men pyelonephritis may follow long-standing prostatic hypertrophy.

Nonobstructive pyelonephritis appears to be more common in females than in males; among 96 cases of pyelonephritic contracted kidney studied at autopsy by Raaschou,[16] 55 per cent of the females and 36 per cent of the males revealed no demonstrable obstructive lesion.

Mechanical factors. These are the most obvious and probably most important factors in the genesis and development of pyelonephritis. Retardation or stasis of the flow of urine anywhere in the urinary channel between the renal pelvis and urethral meatus may result from obstruction, from neuromuscular disturbances or even from atonic changes consequent to long-standing infection.[3,17] Obstructive lesions below the bladder, as in hypertrophy or carcinoma of the prostate and urethral stricture, are associated with a greater incidence of pyelonephritis than is found with obstruction of the ureters above the bladder, such as occurs from ureteral stricture or external compression of the ureters. The difference in frequency of infection in patients with obstruction below the bladder may be due to distention of the bladder and vesicoureteral reflux and the introduction of infection by catheterization, indwelling catheter or instrumentation. Furthermore, there is experimental evidence that urinary stasis increases the susceptibility of the kidney to hematogenous invasion by bacteria.[18]

Impairment of bladder function and consequent urinary-tract infection may occur in a variety of disorders of the nervous system such as diabetic neuropathy, multiple sclerosis, poliomyelitis, spinal-cord injury and tabes dorsalis and after spinal anesthesia. As a result of disturbances in bladder innervation retention of urine occurs. This may be followed successively by vesicoureteral reflux, hydroureter and hydronephrosis. Bacteria, introduced by catheterization and indwelling catheter, may cause urinary-tract infection, with involvement of the kidney.

Iatrogenic implantation of bacteria in the urinary tract. The high incidence of urinary-tract infections after repeated catheterizations, indwelling catheters and instrumentation has been reported by many observers.[1,6,8] Such infections occur more frequently in patients with obstruction of the lower urinary tract than in those with ureteral obstruction or absence of any obstruction. In the presence of established urinary-tract infection catheterizations and instrumentation may be responsible for the introduction of organisms that may be more resistant than those already present. Furthermore, prophylactic drugs administered during catheterization or instrumentation not only may be ineffective in preventing urinary-tract infection but also may be responsible for replacing susceptible with resistant bacteria.[6] The bac-

teremia that follows urethral catheterization or instrumentation may account for the transport of infection to the kidney from the lower urinary tract.

Diabetes mellitus. The high incidence and gravity of pyelonephritis in patients with diabetes has been reported by many observers.[19-21] Renal medullary necrosis, a severe and fulminating form of pyelonephritis, occurs more often in the diabetic patient. The combination of glycosuria, which may favor the growth of bacteria in the urine, and the enhanced susceptibility of the diabetic person to infections may explain the greater incidence of pyelonephritis in this group of patients. Furthermore, the danger of implantation of bacteria in the urinary tract by catheterization of diabetic patients, especially if acidosis is present, has recently been re-emphasized.[19]

Others. The report of Perkoff et al.[22] of hereditary pyelonephritis with progressive renal insufficiency and nerve deafness only in the males of the kindred is unique but contains no data pertaining to the possible pathogenetic factors involved.

The mechanisms by which pyelonephritis develops during the course of severe constipation, diarrhea or ulcerative colitis are poorly understood. Calculi in the kidney or bladder, in addition to causing obstruction, may by direct trauma to mucous membranes contribute to the development of urinary-tract infection.

Very little is known concerning the resistance of the kidney to infection, especially in cases of pyelonephritis in which neither an obstructive lesion nor obvious predisposing factor can be discovered.

Pathology

Current concepts of renal pathology have been presented in the excellent monographs by Weiss and Parker,[15] Bell[17] and Allen.[23] According to the last, pyelonephritis in one of its stages is the most common renal lesion found at autopsy. Furthermore, he states that chronic pyelonephritis is more common than chronic glomerulonephritis and somewhat less common than benign nephrosclerosis. Raaschou[16] found chronic pyelonephritis to be two or three times more often the cause of uremia than glomerulonephritis and about four times more often than benign nephrosclerosis. Pyelonephritis may be acute, chronic or healed and may not be associated with obstruction of the urinary tract and other renal diseases. In addition, it may be unilateral or bilateral and focal or diffuse.

Acute Pyelonephritis

In all cases of acute pyelonephritis, the parenchymatous involvement is similar, regardless of the origin and type of the infection. Acute pyelonephritis is primarily an inflammatory disease of the interstitial tissues consisting of multiple abscesses scattered through both cortex and medulla, wedge-shaped suppurative infarcts with the base toward the cortical surface, infiltrations of the periglomerular and perivascular lymphatics, interstitial tissues, tubules and at times glomeruli by polymorphonuclear leukocytes. Bacteria may be found in the interstitial tissues, tubules and perivascular lymphatics. Acute involvement of the arterioles, with leukocytic infiltration of the wall and thrombosis of the lumen, may occur. The pelvis often shows inflammatory changes of varying degree. In the cases showing resolution and organization of the renal lesions with clinical recovery deep pits on the surface of the kidney develop as a result of cortical atrophy consequent to the destruction of the infiltrated tubules and interstitial tissue. Furthermore, scarring and deformity of the pelvis and papillae may result.

Chronic Pyelonephritis

In bilateral forms of pyelonephritis, the disease is usually more pronounced in one kidney than in the other. In unilateral disease, the atrophy may become extreme, and such a kidney may be confused with congenital hypoplasia.[24]

The more important histologic characteristics are as follows: periglomerular fibrosis; groups of fibrotic glomeruli within the wedge-shaped, atrophic, cortical areas; colloid casts in the tubules, which are lined with atrophic, flattened epithelium; interstitial fibrosis; infiltration of interstitial tissue with lymphocytes and plasma cells; and thickening of the wall of the pelvis by connective tissue. The atrophic and infiltrated areas usually show a patchy distribution. The nonscarred areas of parenchyma may be essentially normal. If the pyelonephritic process is still active infiltration of the tubules and interstitial tissue by polymorphonuclear leukocytes is seen.

Vascular lesions are found in the inflamed and scarred areas and are thought to be due to disuse atrophy. The arteries, according to Bell,[17] show no intimal disease. On the other hand, Weiss and Parker[15] stated that the essential arterial lesion consisted of increased connective tissue in the intima and designated this lesion as "productive endarteritis." All authorities agree upon the other changes affecting the arteries — that is, reduplication of the internal elastic lamina and medial hypertrophy and fibrosis. The arteriolar changes consist of thickening of the walls owing to extreme medial fibrosis associated with replacement of smooth muscle by collagen. In the absence of hypertension no significant vascular lesions are found except in the scarred areas. On the other hand, when hypertension is present, the vascular changes are always more marked and diffuse.[15,25,26]

Renal Medullary Necrosis

This condition, a serious and frequently fatal complication of pyelonephritis, is most often encountered in patients suffering from diabetes or urinary-tract obstruction or both. An excellent review of this sub-

ject was presented recently by Mandel.[21] The lesion resembles an infarct because of the pale color of the involved pyramids and papillae, standing out in sharp contrast against the surrounding parenchyma. Friable necrotic papillae may slough off. Microscopically, coagulation necrosis, dense, purulent exudate and masses of bacteria are seen. Thrombosed blood vessels in and surrounding the necrotic areas have been implicated in the development of the necrosis. After sequestration or resorption of the necrotic material healing with fibrosis may occur occasionally.

Pathologic Physiology

Renal Function

Disturbances in renal function do not occur in acute unilateral pyelonephritis. On the other hand, in acute diffuse bilateral pyelonephritis, nitrogen retention may develop occasionally, only to disappear with recovery. In chronic bilateral pyelonephritis the degree and progress of impairment of renal function depend on and vary with the extent of parenchymatous suppuration and scarring. Moderate nitrogen retention may be present for many years. Fluctuation in renal function occurs in chronic pyelonephritis more often than in any other type of renal disease and is related to the development and subsidence of exacerbations. Weiss and Parker[15] observed several patients with uremia associated with coma and pericarditis in whom, after recovery from the uremia, renal function was adequate for several years.

Disturbances of tubular function in chronic pyelonephritis, with consequent acidosis and inability to conserve electrolytes, may be responsible for a variety of clinical conditions including deToni–Fanconi syndrome, osteomalacia, Milkman's syndrome, "salt-losing nephritis," low-potassium syndrome, secondary hyperparathyroidism, renal rickets and infantilism and osteosclerosis.[27-31]

Cardiovascular Phenomena[22]

Hypertension. The blood pressure is normal in acute pyelonephritis unless hypertension was preexistent. Hypertension of varying severity is observed in many cases of chronic bilateral pyelonephritis when renal function is normal or when impaired kidney function and renal insufficiency exist. Unilateral pyelonephritis may occur with or without hypertension. It is noteworthy that patients with uremia may have normal blood pressure.

In cases of malignant hypertension studied at autopsy Weiss and Parker[15] found 15 to 20 per cent, and Schottstaedt and Sokolow[33] reported 12 out of 35 cases were on a pyelonephritic basis.

The cause of the elevated blood pressure remains unexplained.

Although cardiac enlargement and congestive heart failure may develop in patients with pyelonephritic hypertension, coronary arteriosclerosis and cerebrovascular accidents are rare.[15,34] In adults and older patients primary hypertension may precede the onset of pyelonephritis and may be associated with coronary and cerebral arteriosclerosis; angina pectoris, coronary failure and myocardial infarction, as well as congestive heart failure and cerebrovascular accidents, may occur.

Oliguria and Anuria

Oliguria or anuria may develop during the course of severe bilateral pyelonephritis complicated by renal medullary necrosis. Anuria may follow cystoscopy in patients with pyelonephritis.[35]

Natural History of Pyelonephritis

In 1933 Longcope and Winkenwerder[36] presented a historical survey of the literature pertaining to the pathological and clinical features of nonobstructive bilateral pyelonephritis, as well as an account of the natural history and clinical significance of the disease based on long-term follow-up study of 9 patients. In 1937 Longcope[37] reported his findings based on a continuous study of 22 cases of chronic nonobstructive bilateral pyelonephritis and elaborated further on the natural history and clinical significance of the disease. Both papers of Longcope are strongly recommended as excellent samples of clinical research presented in simple and effective language. Weiss and Parker,[15] in 1939, presented a clinical and morphologic study of 100 cases of nonobstructive pyelonephritis in various stages from the acute to the terminal chronic or healed, with special emphasis on the chronic stage of the disease as well as on the characteristics of vascular lesions occurring in chronic pyelonephritis and their relation to arterial hypertension. The contributions of these authors and others[38,39] have helped to clarify the natural history of pyelonephritis.

Certain aspects of the variable clinical course of the disease may be summarized briefly:

Pyelonephritis may appear as a clearly defined acute illness with characteristic symptoms of pain in the flank or costovertebral region, frequency and burning on urination, chills, fever, headache, prostration, gastrointestinal disturbances, abdominal distention and ileus.

Repeated symptomatic flare-ups of pyelonephritis may occur. Urinary abnormalities and bacteriuria may be found only during the acute episodes or continuously throughout the symptom-free intervals between attacks.

Recurrent bouts of nonspecific symptoms, such as fever and myalgias, may occur. Urinary abnormalities and bacteriuria are often found continuously in these patients.

Pyelonephritis may be asymptomatic until advanced renal insufficiency appears, when weakness, anemia and other phenomena of uremia supervene.

Pyuria, bacteriuria and proteinuria may be continuously present in the absence of any symptoms. Occasionally, the patient may give a history of passing cloudy urine from time to time for many years.

Benign hypertension and its consequences — such as cardiac enlargement and congestive heart failure — may appear at any time during the long course of pyelonephritis. In a small number of patients, malignant hypertension supervenes.

Fulminating renal failure may occur during an acute exacerbation or after catheterization or instrumentation of the urethra, bladder or ureters.

Most cases of acute pyelonephritis and some cases of chronic pyelonephritis heal.

The course an individual patient with pyelonephritis will follow is unpredictable.

Certain pertinent aspects of the variable pathologic course of the disease may be stated briefly as follows:

Pyelonephritis consists of single, repeated or continuous attacks of bacterial inflammation of the renal parenchyma. The resultant structural lesions may vary from a single to many focal areas or diffuse involvement of one or both kidneys. Scarring and fibrosis represent the end stages of bacterial invasion. The degree and extent of scarring depend upon the severity and duration of the bacterial infection of the renal parenchyma.

If hypertension, benign or malignant, supervenes during the course of pyelonephritis, a "vascular factor" is added that may contribute to further destruction of the renal tissue.

After consideration of the clinical and pathological aspects of pyelonephritis mentioned above, it is apparent that this disease may develop and progress during many years with or without symptoms, but usually with urinary abnormalities.

(To be concluded)

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MEDICAL INTELLIGENCE

UROLOGIC EXAMINATION WITH THE NEW RADIOPAQUE MEDIUMS, DIATRIZOATE, ACETRIZOATE AND DIPROTRIZOATE*

A Clinical Comparison

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AMONG the more recently developed iodinated contrast mediums for radiologic delineation of the urinary tract and demonstration of uropathic processes are sodium diatrizoate,** sodium acetrizoate†† and sodium diprotrizoate.‡‡ The increased use of intravenously administered materials for roentgenographic visualization has actuated the search for compounds free of the hazard of severe sensitivity or toxic reactions. Since it is the concern for the safety of the patient that has served as a deterrent to the widespread use of intravenous urography as a routine examination procedure, a low incidence of deleterious effects is as important as radiographic contrast in the evaluation of new urographic substances. The experience with diatrizoate, acetrizoate and diprotrizoate presented in this paper has been appraised with these major criteria in mind although such other factors as prompt and complete excretion and lack of tissue-irritating properties contribute to the characterization of a good contrast medium.

Of the three mediums considered in this comparative study, acetrizoate in various concentrations has been longest in clinical use, and diprotrizoate has been most recently introduced. Urograms of diagnostic quality have been obtained in a high percentage of patients with both compounds.[1,2] Similar results with diatrizoate have been noteworthy for the remarkably few untoward reactions of any type that have occurred after its use intravenously.[3,4] A previous series of 100 intravenous pyelograms obtained at this institution with diatrizoate exhibited a significant improvement in film contrast, and the patients so examined experienced a minimum percentage of reactions to this medium.[5] Since that time 30 retrograde pyelographic examinations have been carried out with diatrizoate; these data are also presented in this report.

TABLE 1. *Age and Sex Distribution of Patients Examined.*

AGE GROUP	DIATRIZOATE NO. OF CASES	ACETRIZOATE NO. OF CASES	DIPROTRIZOATE NO. OF CASES
yr.			
0 - 10	5	—	1
11 - 20	—	2	2
21 - 30	8	4	1
31 - 40	4	2	—
41 - 50	6	4	1
51 - 60	10	6	4
61 - 70	7	13	8
71 - 80	7	10	2
81 - 90	3	1	1
Totals	50	42	20
SEX DISTRIBUTION			
Males	28	20	11
Females	22	22	9

Excretory pyelograms were obtained with diatrizoate in 50, with acetrizoate in 42 and with diprotrizoate in 20 cases. The age and sex distributions within these groups is shown in Table 1.

Commercially available 50 per cent solutions of each contrast medium were administered intravenously, in 20-ml. quantities, to all but 1 patient, who was given diatrizoate intramuscularly. All films were examined by our group of urologists and radiologists, and were graded for the quality of contrast and the clarity with which urinary structures were defined. The pyelograms were adjudged excellent, good, fair or poor, those in the first three classifications being of diagnostic character. Qualitative results of this procedure are presented in Table 2.

Thus, it appears from results achieved with these small groups of patients that a high degree of efficiency may be attributed to all three contrast mediums and that pyelograms of diagnostic value may be anticipated in more than 96 per cent of the cases in which they are employed. In previous work with diatrizoate[5] 30-ml. doses used routinely were found to produce effective shadows in a majority of 100 patients. No appreciable distinction could be made, however, in the radiographic density of films obtained

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with the uniform 20-ml. dose employed for this comparative study and those seen earlier. The lower dose is justified, therefore, for the reduced likelihood of undesirable effects.

Significant differences between the urographic compounds were observed in the number and severity of untoward reactions during or soon after intravenous administration (Table 3). Although only 2 of the 50 (4 per cent) patients examined with diatrizoate showed mild reactions to the medium, 17 of the

TABLE 2. *Comparative Quality of Excretory Pyelograms Obtained with Three Contrast Mediums.*

RESULT	PATIENTS ON DIATRIZOATE		PATIENTS ON ACETRIZOATE		PATIENTS ON DIPROTRIZOATE	
	NUMBER	PERCENTAGE	NUMBER	PERCENTAGE	NUMBER	PERCENTAGE
Excellent	23	46	17	40.0	7	35
Good	20	40	20	47.6	13	65
Fair	5	10	4	9.5	—	
Poor	2*	4	—	†	—	
Totals	50		41		20	

*One exhibited high nonprotein nitrogen.
†No pyelogram obtained in 1 patient since injection of acetrizoate discontinued owing to severe venous cramp.

42 (40 per cent) given acetrizoate and 4 of the 20 (20 per cent) given diprotrizoate exhibited both mild and severe expressions of intolerance. In 1 patient acetrizoate induced side effects sufficiently severe to require discontinuation of the injection. All patients were questioned for positive allergic histories, but no definite correlation could be demonstrated between pre-existing allergy and a predisposition to react unfavorably to these contrast mediums. Antihistamines were not administered to any patient in this series.

In addition to the intravenous studies presented, retrograde examinations with 50 per cent diatrizoate were carried out in a group of 30 patients, 21 males and 9 females, ranging in age from five to seventy-five years. According to pelvic capacity the medium was injected in quantities of 3 to 20 ml. Films were evaluated as with the intravenous procedures, with the following results: excellent visualization was obtained in 8 cases, representing 26.6 per cent of the total number; visualization was good in 14 cases, or 46.6 per cent, fair in 7 cases, or 23.3 per cent, and poor in 1 case, or 3.3 per cent, of the total (Table 4). Although 4 patients in the series had a history of allergy, no untoward reactions to the medium were observed.

On the basis of this experience in both intravenous and retrograde pyelographic procedures diatrizoate appears to be a highly efficient medium for the roentgenographic visualization of the urinary tract. Its particular advantage over other available contrast substances for intravenous administration is the relative safety with which it may be used, as evidenced by the fewer untoward reactions occurring during this study.

DISCUSSION

The newly synthesized iodinated contrast mediums have contributed significantly to the accurate diagnosis of urologic lesions and physiologic disturbances of the urinary system by providing for interpretation more clearly and sharply defined roentgenograms. With the increased utilization of intravenous excretory urographic technics, concern for the safety of the patient has increased simultaneously, particularly since the newer compounds demonstrate approximately equal efficiency. This study was undertaken to compare diatrizoate, acetrizoate and diprotrizoate, three commonly used, commercially available mediums, both for the quality of the contrast they produced and for the incidence and intensity of untoward reactions associated with their use.

TABLE 3. *Untoward Reactions.*

	REACTION	PATIENTS ON DIATRIZOATE		PATIENTS ON ACETRIZOATE		PATIENTS ON DIPROTRIZOATE	
		NUMBER	PERCENTAGE	NUMBER	PERCENTAGE	NUMBER	PERCENTAGE
Intensity:							
	Mild	2	4	9	21	1	5
	Severe	0	—	8*	19	3	15
	Totals	2		17		4	
	Averages		4		40		20
Type:							
	Nausea		1		4		2
	Vomiting		1		4		—
	Flushing of skin		—		1		—
	Venous cramp		—		7		3
	Hives		—		1		—
	Local erythema		—		1		—
	Numbness of arm		—		1		—
	Choking sensation		—		1		1
	Dyspnea		—		1		—
	Profuse sneezing		—		1		—

*One reaction sufficiently severe to require discontinuation of injection.

All three preparations proved highly efficient diagnostic aids. Previous experience with diatrizoate had indicated a low percentage of undesirable effects, and this earlier observation was confirmed by this study. Compared with acetrizoate and diprotrizoate, diatrizoate produced considerably fewer expressions of intolerance when administered in equal doses. Injection of acetrizoate was discontinued in 1 patient because of the severity of side effects. Although smaller groups of patients have been involved in this evaluation than in another comparison between diatrizoate and acetrizoate reported,[4] the results of both studies agree that diatrizoate is relatively safe.

Although preliminary ocular, oral, dermal or intravenous sensitivity testing is generally recommended as a precautionary measure against severe or even fatal reactions to contrast mediums, these procedures are not infallible. It has not been possible in our limited groups of patients to observe any relation between a history of allergy and a predisposition to react unfavorably to any of the mediums tested. In view of the unpredictability of the response, selection of the substance least toxic to human patients remains the most effective preventive measure. At present diatrizoate appears to fill this requirement.

The high radiopacity of diatrizoate favors greater urographic clarity in retrograde procedures when excretory pyelography is contraindicated. Only 1 of 30 pyelograms in this series was inadequate for diagnostic use. No reactions to the medium occurred although 4 patients had a previous history of allergy.

Table 4. *Quality of Retrograde Pyelograms Obtained with Diatrizoate in 30 Cases.*

Age Distribution	Total No. of Cases	Excellent Results	Good Results	Fair Results	Poor Results
		no. of cases	no. of cases	no. of cases	no. of cases
yr.					
5 - 20	2	1	1	0	0
21 - 50	10	2	5	3	0
51 - 75	18	5	8	4	1
Totals	30(100.0%)	8(26.7%)	14(46.7%)	7(23.3%)	1(3.3%)

Summary and Conclusions

Comparative urologic examinations carried out with small groups of patients with the new radiopaque substances, diatrizoate, acetrizoate and diprotrizoate demonstrated all three to be highly efficient intravenous contrast mediums for radiologic delineation of the urinary tract. Of the three, however, diatrizoate produced fewer and less severe untoward reactions, and for this reason is considered most suitable for intravenous use. When intravenous technics are contraindicated, diatrizoate is an efficient medium for retrograde pyelography.

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CASE RECORDS
OF THE
MASSACHUSETTS GENERAL HOSPITAL

Weekly Clinicopathological Exercises

FOUNDED BY RICHARD C. CABOT

BENJAMIN CASTLEMAN, M.D., *Editor*

VIRGINIA W. TOWNE, *Assistant Editor*

CASE 42331

PRESENTATION OF CASE

A fifty-one-year-old woman entered the hospital because of diarrhea.

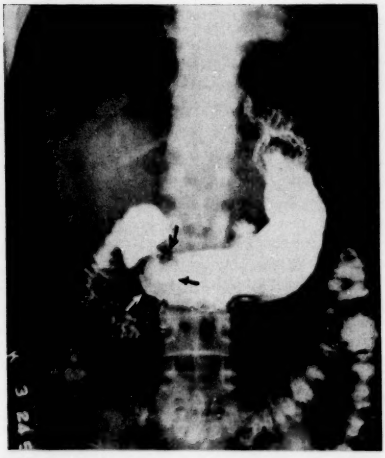

FIGURE 1. *Roentgenogram from the Gastrointestinal Series, Showing a Flat, Shallow Defect of the Gastric Antrum Causing No Interference with Peristalsis.*

For ten years before admission she had had recurrent episodes of diarrhea associated with nervousness. Sometimes, the diarrhea was accompanied by vague abdominal cramps. Occasionally, there was mild nausea but no vomiting. There was no melena, chills or fever. There was intermittent "heartburn" that was occasionally relieved by antacids. During the five years before entry she was said to have been mildly anemic and had taken iron irregularly. Three months before admission because of "heartburn" and loss in weight she was given a low-roughage diet with phenobarbital and belladonna, with relief of gastrointestinal symptoms and a gain in weight. An upper gastrointestinal series at that time was said to have revealed a gastric lesion. An appendectomy was performed thirteen years before admission.

Physical examination showed a well nourished woman in no distress. Examination of the abdomen revealed a healed appendectomy incision. No masses were felt.

The temperature was 98.2°F., the pulse 72, and the respirations 20. The blood pressure was 110 systolic, 70 diastolic.

The urine gave a + test for albumin; the sediment contained occasional red cells, 10 white cells and a moderate number of bacteria per high-power field. Examination of the blood revealed a hemoglobin of 13.2 gm. per 100 ml. and a white-cell count of 10,400. The serum nonprotein nitrogen was 29 mg., the total protein 6.2 gm., the albumin 4.1 gm., the globulin 2.1 gm., and the fasting blood sugar 82 mg. per 100 ml. The alkaline phosphatase was 0.6 units. The prothrombin content was 83 per cent. The blood Hinton test was positive. Gastric analysis showed no free acid after alcohol and histamine. Of two cytologic examinations of the gastric contents for malignant cells, one was doubtful and the other negative. A stool specimen was normal in color and gave a negative guaiac test. An upper gastrointestinal series showed a very poorly visualized, somewhat lobulated, rounded, 3-cm. filling defect with a central, poorly visualized pooling of barium measuring almost 1 cm. (Fig. 1 and 2); on some films this lesion was not seen; the duodenal cap showed slight narrowing and deformity of its midportion, without evidence of an active ulcer.

FIGURE 2. *Spot Film of the Gastric Antrum, Showing the Mucosal Detail with Absence of the Normal Folds and the Circular Area Outlined by the Arrows.*

On the ninth hospital day an operation was performed.

Differential Diagnosis

Dr. Daniel S. Ellis*: The problem in this case seems to be: What was the lesion in the stomach that was demonstrated in the x-ray films? I doubt if the patient's history of gastrointestinal symptoms of ten years' duration had anything to do with the lesion in the stomach. The question of whether or not she had any renal disease should also be raised. If any was present, I do not think that it was related to the major problem. Was the urinary specimen analyzed obtained by catheter or voided? If it was a single voided specimen, I should say nothing more about the findings.

Dr. Benjamin Castleman: I think that it was a voided specimen.

Dr. Ellis: This patient came into the hospital because of the diarrhea, and in the course of the workup she was found to have a lesion in the stomach. Is there any information about the x-ray films taken before admission that were said to show a lesion?

Dr. Castleman: No.

Dr. Ellis: Perhaps Dr. St. Aubin will point out the lesion in the stomach.

Dr. Paul M. G. St. Aubin: Two gastrointestinal examinations were carried out two days apart. The first was complemented by a small-bowel examination. Within the antrum of the stomach at its distal end on the lesser curvature is a circular, flat, fairly well defined filling defect (Fig. 1). It has a smooth left margin and a slightly more nodular right margin. Within the center is a round pool of barium that appears to be a shallow ulceration. The majority of the films were taken in the prone position. In the double-contrast study of the antrum taken with the patient supine the rounded filling defect and the irregularity of the prepyloric region of the lesser curvature are again noted (Fig. 2). The shallow depression is not observed. This suggests that it is a structure lying on the anterior aspect of the antrum and extending up to the region of the lesser curvature. The remainder of the gastrointestinal study is negative. The small-bowel examination shows no abnormality except possibly some deformity of the duodenal bulb.

Dr. Ellis: Would you be willing to say whether this lesion has any characteristics that make you think that it might be malignant?

Dr. St. Aubin: I should be inclined to think it is benign because it has a somewhat smooth-appearing surface.

Dr. Ellis: Do you think that the lesion is submucosal?

Dr. St. Aubin: The smooth surface certainly suggests that it is submucosal.

Dr. Ellis: The history is scarce: I suspect that it was written up by a surgeon because a great deal of information that an internist would like has been omitted.

*Assistant physician, Massachusetts General Hospital.

Dr. Robert S. Palmer: The history was not taken by a surgeon; it was a complete one. I shall undertake to supply any information that you wish.

Dr. Ellis: I should like to know more about the treatment of the diarrhea and whether or not it responded to simple antispasmodic therapy and reassurance. Did the patient at any time have liver injections or vitamin B_{12}, in addition to the iron, which might have influenced the picture of the blood?

Dr. Palmer: This woman was studied and treated outside the hospital as most patients can be. She had been a hard-working housewife who passed "loosish" stools, sometimes three or four times a day, and had discomfort and cramps in the lower part of the abdomen. I cannot remember now specifically whether she had liver injections. She had been anemic and had received various preparations of vitamins and iron; perhaps she received liver by mouth. She had been well except for fatigue, the passing and belching of a great deal of gas and a low state of mind. She was promptly and almost completely relieved by belladonna, phenobarbital and a bland, high-calorie diet. Because she had had upper intestinal discomfort and belching, the upper gastrointestinal x-ray films were done to be sure that all the possibilities were covered; they revealed an abnormal finding in the lower end of the stomach. That finding was the thing that brought her into the hospital, not the diarrhea.

Dr. Ellis: Was there evidence historically or on physical examination that the patient had ever had syphilis? Had she ever been treated or had signs of tertiary syphilis?

Dr. Palmer: No.

Dr. Ellis: The only clue to the diagnosis, other than the information that she was a tense, hard-working housewife who may have had increased gastrointestinal motility, is the note that on at least one occasion she had achlorhydria. Rarely, achlorhydria may result in diarrhea. Was this ever checked? Did she have more than one gastric smear?

Dr. Palmer: So far as I know only one had been done.

Dr. Ellis: I think that the patient had functional diarrhea. The achlorhydria and the polypoid filling defect in the stomach make one wonder whether she also had pernicious anemia, with one or more polyps in the stomach. The facts that there was no history of her having been treated with liver or vitamin B_{12}, that she was given iron and that on admission she was not very anemic make me believe that pernicious anemia with gastric polyps is one of the less likely possibilities.

Nothing in the history suggests that this was a malignant lesion. She had not lost weight and had felt well except for the diarrhea; there was no palpable mass and no significant anemia. The only finding suggestive of a neoplasm is the achlorhydria.

The x-ray appearance of the lesion and the history as given make me suspect that she did not have a malignant lesion.

The differential diagnosis is one of the nonmalignant tumor masses in the stomach. Leiomyoma, neurofibroma, aberrant pancreas and lipoma are a few of the more common ones. The question of the serologic test, I suspect, was interposed in the hope that I should say something about a gumma of the stomach. In the last six months there has been a patient in the hospital in whom this lesion was suspected; in fact the patient had other evidence of tertiary syphilis. The lesion in the stomach, which was ulcerated, was similar to the one in the patient under discussion, and it improved on antisyphilitic therapy but did not disappear. That patient was operated on, and the pathologist has yet to tell us what the lesion was. The patient under discussion could have had a gumma of the stomach, but I think it would be most unusual. Firstly, that is a very rare lesion; documenting unequivocal proof of its existence has been scarce since it was first recognized. Secondly, it is most unusual in the absence of other signs of tertiary syphilis. However, nothing about the configuration of the lesion in the x-ray films would allow one to differentiate this lesion from the other possibilities.

A leiomyoma with an ulceration is possible. Patients with this lesion frequently present bleeding as their chief symptom. This lesion cannot be differentiated from the other possibilities.

Lipoma is in the same category, although perhaps less frequent than the other two. Ulceration in a lipoma is almost unheard of. The pooling of barium in the middle of the rounded mass suggests an ulceration.

Aberrant pancreas can produce a lesion similar to this and may actually ulcerate or may have folds and convolutions that simulate ulcerations. These are the main diagnoses to consider. I know of no clues in the protocol or from the x-ray films, short of exploring the patient, on which to make a positive diagnosis. We see leiomyoma not infrequently so I cannot believe that Dr. Castleman would pick this out for a clinicopathological case. Therefore, I wonder whether it was one of the rarer forms of benign tumors of the stomach, probably submucosal with an ulceration in it. Of those that I have mentioned lipoma, gumma, neurofibroma and aberrant pancreas are the more likely possibilities. One could try all sorts of therapeutic measures, but unless the mass disappeared entirely, the patient would have to be operated on. I think that the lesion was probably a benign submucosal tumor of the stomach with an ulceration in it, and I shall pick lipoma as a first guess because this is a clinicopathological case and because an ulcerated lipoma of the stomach is a rare disease.

DR. CASTLEMAN: Dr. Fleischner, will you comment on the films? Dr. Fleischner is visiting the hospital today.

DR. FELIX FLEISCHNER*: The possibility of a malignant process should be considered. I think I should subscribe to Dr. Ellis's conclusion that the patient should have been operated on.

DR. JOHN W. STOKES: I should like to ask Dr. Ellis whether a carcinoid tumor would occur in this location.

DR. ELLIS: Anything can happen, but I think that that is one of the less likely possibilities.

DR. CASTLEMAN: Carcinoids do occur in the stomach. The ones that I have seen or read about were much smaller.

DR. PALMER: The patient was happy about having been relieved by the improvement in hygiene, the antispasmodics and phenobarbital. Then the x-ray report revealed the lesion with ulcerations. So she came into the hospital for studies and a decision. In the hospital the first x-ray films were reported as, if not normal, all but normal. The other x-ray films, therefore, were brought in, and the radiologists were asked to have another look. The second written report and the verbal report were that it was doubtful if there was an ulceration. (Correct me if I am wrong.) It was suggested that we observe her for a few weeks. So we had to make a decision on one equivocal cytologic report and mostly on varying x-ray reports. The patient felt well and wanted to know why she was in the hospital. I attended Dr. McKittrick's operation with diagnostic fear and trembling! The serologic examinations have not been completed; we are rechecking these.

DR. CASTLEMAN: I can read the official x-ray report of the second examination:

> Although tumor cannot be excluded with complete certainty, if it is present it is probably quite superficial and spreading in type. The central pooling of barium suggests that a healing crater, a superficial ulcerated spreading carcinoma, is a possibility. Another possibility is an ulcer with a large area of surrounding edema. A spindle-cell tumor or aberrant pancreas seems rather unlikely in view of the slight degree of protrusion into the stomach lumen. There seems to be a slight deformity of the duodenum suggesting old ulcer in the past.

CLINICAL DIAGNOSIS

?Ulcer of stomach.
?Carcinoma of stomach.

DR. DANIEL S. ELLIS'S DIAGNOSIS

Lipoma of stomach, with ulceration.

ANATOMICAL DIAGNOSIS

Adenocarcinoma-in-situ of stomach.

PATHOLOGICAL DISCUSSION

DR. CASTLEMAN: At operation Dr. McKittrick palpated the diseased area of the stomach between his thumb and finger and could feel a thickening that seemed to be within the mucosa. He did not see any

*Director, Department of Radiology, Beth Israel Hospital.

previous scarring of an ulcer; he opened the stomach and saw what looked like a fold of greatly thickened mucosa that extended around the stomach posteriorly, being present on both the greater and lesser curvatures; there was no obvious ulceration. He removed that segment, which measured about 2.5 by 1 cm., for pathological examination.

In the gross there was no definite ulceration, but there was an area, about the size that was pointed out in the x-ray films, in which the mucosal folds were thick and raised and seemed to surround folds in the center that were slightly depressed. The mucosa in that area had a granular surface without a true ulceration. A section through that area, on frozen section and in the fixed section, showed adenocarcinoma. The carcinoma had not extended beyond the muscularis mucosae. I believe this is an example of adenocarcinoma-in-situ involving the mucosa and just beginning to extend into the muscularis mucosae, which is still mucosa. All the patients whom we have had in the past who had such lesions have been cured by resection.

DR. JACOB LERMAN: Were any lymph nodes palpated?

DR. CASTLEMAN: No lymph nodes were palpated. The question is whether the surgeon should reoperate and remove more of the stomach. He removed a large segment, and we believe that there was a large margin proximally and sufficient distally — he had gone to the pylorus — to make reoperation unnecessary.

CASE 42332

PRESENTATION OF CASE

First admission. A forty-year-old laborer entered the hospital because of nausea and vomiting.

One month previously he noted easy fatigability, drowsiness and anorexia. There was a transient episode of blurred vision. One week later persistently dark urine was noted. The urinary output remained at about 1 liter per day. There was conjunctival injection and slight periorbital edema. Two weeks before admission he noted severe pain and tenderness in the muscles of the thighs and in the knees, without any associated heat, erythema or swelling. Subsequently, there was persistent nausea, with "gnawing" epigastric distress and episodes of vomiting. On several occasions he either coughed up or vomited a cupful of blood. Severe frontal headaches were noted. During the week before entry there was nocturia (twice). Six days before admission the temperature was 100°F. During the five days before entry there were episodes of coughing, exertional dyspnea and respiratory wheezing that were treated by his physician with sulfonamides and penicillin. He had lost 20 pounds in weight during the month before admission.

Four years previously he was admitted to another hospital for three days because of urticaria, fever, shaking chills, malaise, arthralgia and generalized lymphadenopathy that occurred a week after an injection of tetanus antitoxin given because of a minor injury. Thereafter, he remained well until the present illness. There was no history of renal disease, hypertension or rheumatic fever.

Physical examination revealed a well nourished, pale man of athletic physique who complained of a headache. The respirations were rapid and shallow. The joints were normal. Except for shotty axillary lymph nodes there was no lymphadenopathy. There was periorbital edema, and the conjunctivas were injected. Examination of the optic fundi showed some blurring of the disk margins, with peripapillary superficial hemorrhages bilaterally and an old chorioretinitis in the right fundus. The lungs were normal. The heart was not enlarged. There was a normal sinus rhythm at a rate of 84. The aortic second sound was greater than the pulmonic. No murmurs were audible. Examination of the abdomen showed epigastric tenderness. The edge of the liver, which was not palpable, was percussed 2 fingerbreadths below the right costal margin. The spleen was not felt. Slight puffiness of the hands was noted. There was no edema of the ankles. Neurologic examination was negative.

The temperature was 100.8°F., the pulse 84, and the respirations 40. The blood pressure was 125 systolic, 75 diastolic.

The urine, which was smoky brown, had specific gravities that ranged between 1.008 and 1.013 and gave a ++++ test for albumin; the sediment contained 3 to 10 white cells, numerous red cells, 10 to 15 granular casts and 0 to 3 red-cell casts per high-power field; a culture showed no growth. The urinary urobilinogen was 0.4 Ehrlich unit. The excretion of sodium was 138 milliequiv., the potassium 38 milliequiv., the chloride 30 milliequiv., and the total solutes 375 milliosmols per liter per twenty-four hours. Examination of the blood revealed a hemoglobin of 6.4 gm. per 100 ml., a hematocrit of 25 per cent and a white-cell count of 10,900, with 84 per cent neutrophils and 16 per cent lymphocytes. The nonprotein nitrogen was 76 mg., the total protein 4.9 gm., the albumin 3.1 gm., the globulin 1.8 gm., the bilirubin 0.8 mg., the calcium 8.8 mg., the phosphorus 5 mg., the cholesterol 195 mg., and the fasting blood sugar 130 mg. per 100 ml. The serum sodium, the potassium, the chloride and the carbon dioxide were normal. The prothrombin content was 100 per cent. The bromsulfalein retention was 16 per cent. The serum electrophoretic pattern was normal. The Coombs test and the blood Hinton test were negative. Bleeding and clotting times were normal. An L.E.-cell preparation was negative. Blood cultures showed no growth. Numerous stool specimens gave a negative guaiac test. A culture of the sputum grew out a few coliform bacilli and *Neisseria catarrhalis*. A cul-

ture of the nose grew out abundant *Staphylococcus aureus* and a culture of the throat grew out abundant alpha-hemolytic streptococci and moderate *Staph. aureus*. X-ray films of the chest taken on the third hospital day demonstrated a diffuse patchy homogeneous density throughout both lung fields; the vessels in the hilar regions were prominent; the heart was enlarged in all chambers (Fig. 1). An abdominal

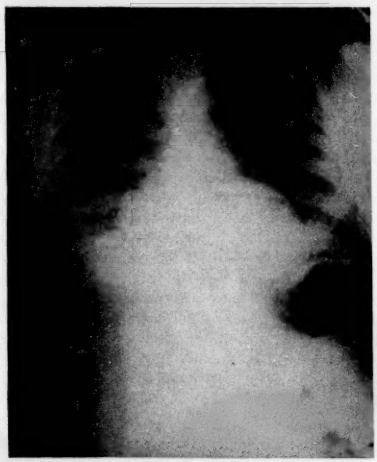

FIGURE 1. *Roentgenogram of the Chest.*

film was normal. An electrocardiogram showed a normal sinus rhythm at a rate of 84; the PR and QRS intervals were 0.16 and 0.09 seconds, respectively; the axis was normal; the T waves were low in the limb leads and in Leads V_5 and V_6.

Shortly after admission, during an intravenous infusion, moist basal pulmonary rales that subsequently cleared became audible. The patient continued to have dyspnea, myalgia, nausea, vomiting and episodes of pain involving the right-temporomandibular and right-shoulder joints. From time to time basal pulmonary rales were heard. There was no distention of the veins of the neck. With Meticorten therapy, 100 mg. daily, there was a dramatic relief of symptoms. After about a week there was a marked, persistent diuresis with a urinary output up to 5 liters per twenty-four hours. Biopsy of a gastrocnemius muscle on the thirteenth hospital day showed arteriolar sclerosis and a few focal areas of lymphocytic infiltration in the interstitial tissue. The serum nonprotein nitrogen gradually rose to 210 mg. per 100 ml. by the twentieth hospital day. At this time examination of the optic fundi showed the previously noted hemorrhages to be resolving; in addition definite thickening of the walls of the vessels was noted. Electrocardiograms showed some improvement in the previously noted changes in the T waves. During the next eight weeks the nonprotein nitrogen gradually fell to a range of 50 to 75 mg. per 100 ml. The hematuria and proteinuria persisted. The urinary electrophoretic pattern showed most of the protein to be albumin. The urinary excretion of sodium ranged between 12 and 42 milliequiv., the potassium between 15 and 59 milliequiv., the chloride between 20 and 64 milliequiv., and the total solutes between 320 and 370 milliosmols per liter per twenty-four hours. The creatinine clearance ranged between 22 and 66 liters per day. The serum calcium ranged between 7.2 and 8.4 mg., the phosphorus between 5.7 and 7.5 mg., and the cholesterol between 241 and 270 mg. per 100 ml. There were periodic episodes of nausea and vomiting that subsided with a bland diet and Thorazine. When the dosage of Meticorten was gradually reduced to 10 mg. daily there was recurrence of pain and tenderness in the right shoulder and tenderness of the hamstring and gastrocnemius muscles. With an increase in the dosage of Meticorten to 50 mg. daily the pain and tenderness subsided. On the sixty-third hospital day puffiness of the face and ascites that had subsided with restriction of intake of salt and water recurred. The optic fundi showed no further changes, and the blood pressure remained within normotensive levels. During the hospital course ten transfusions of blood were given. The hematocrit ranged between 26 and 33 per cent. The patient was discharged on the sixty-sixth hospital day on a low-salt diet, Serpasil, Thorazine and Meticorten, 50 mg. daily.

Second admission (two weeks later). In the interval he was asymptomatic with limited activity until three days before entry, when there was the sudden onset of edema of the legs and periorbital regions, moderate dyspnea, diffuse tremulousness, severe intractable nausea, vomiting of blood-stained gastric contents and muscular cramps without carpopedal spasm. During the two days before admission he was unable to take any medication.

Physical examination revealed a dyspneic, pale, tremulous, retching man with periorbital edema. The optic fundi showed marked thickening of the walls of the vessels near the disks, with white exudates and old hemorrhages. Examination of the heart and lungs was negative. There was slight tenderness at the right costovertebral angle and in the epigastrium. Slight pretibial edema was noted.

The temperature was 99.4°F. by rectum, the pulse 78, and the respirations 20. The blood pressure was 170 systolic, 110 diastolic.

The urine gave a ++++ test for albumin, and the sediment contained 10 to 20 red cells per high-power field. Examination of the blood revealed a hemoglobin of 8.5 gm. per 100 ml. and a white-cell count of 8400, with 81 per cent neutrophils, 10 per cent lymphocytes, 5 per cent monocytes and 4 per

cent eosinophils. The nonprotein nitrogen was 120 mg., the calcium 7.6 mg., and the phosphorus 7.2 mg. per 100 ml.

With Amytal given intramuscularly and Thorazine the patient became asymptomatic. After four transfusions of blood the hemoglobin rose to 10.6 gm. per 100 ml. He was discharged improved on the third hospital day on previous medication, including Meticorten, 50 mg. daily.

Final admission (eleven days later). He continued to be dyspneic on exertion. Four days before entry the blood pressure was 190 systolic, 120 diastolic. The hemoglobin was 8 gm. per 100 ml. Two days later there was increasing peripheral edema, as well as persistent severe nausea and vomiting. He noted pain in the right paravertebral region that at times was exaggerated by deep respirations.

Physical examination showed peripheral edema. The lungs were normal. The heart was not enlarged. A Grade 1, high-pitched, systolic murmur was audible along the left sternal border.

The temperature was 98.6°F., the pulse 72, and the respirations 20. The blood pressure was 160 systolic, 106 diastolic.

The urine gave a ++++ test for albumin; the sediment contained numerous granular, cellular and hyaline casts and numerous white cells and red cells per high-power field; a culture grew out moderate pneumococci and *Staph. aureus* and a few beta-hemolytic streptococci. The creatinine clearance was 8.2 and 5.2 liters per twenty-four hours. Examination of the blood revealed a hemoglobin of 11.2 gm. per 100 ml. and a white-cell count of 15,000, with 92 per cent neutrophils. The nonprotein nitrogen was 190 mg., the total protein 4.4 gm., the albumin 2.6 gm., the globulin 1.8 gm., the calcium 7.1 mg., the phosphorus 8.6 mg., the bilirubin 0.2 mg., the creatinine 11.8 mg., the cholesterol 420 mg., and the fasting blood sugar 89 mg. per 100 ml. The serum sodium was 132 milliequiv., the potassium 4.8 milliequiv., the chloride 93 milliequiv., and the carbon dioxide 17 milliequiv. per liter. The prothrombin content was 83 per cent. The alkaline phosphatase was 2 units. The amylase was 32 Russell units. The Coombs test was negative. The serum electrophoretic pattern was normal. Culture of the nose grew out abundant pneumococci and nonhemolytic streptococci. Culture of the throat grew out abundant pneumococci, alpha-hemolytic streptococci and nonhemolytic streptococci. A blood culture was negative. X-ray films of the chest demonstrated generalized cardiac enlargement, prominent pulmonary vascular markings and some areas of patchy density, particularly in the right-lower-lung field. An abdominal film was normal.

With Thorazine and Amytal given intramuscularly and continuation of Meticorten there was improvement in the symptoms except for intermittent episodes of retching. On the tenth hospital day there was severe dyspnea on exertion, orthopnea, pain in the muscles and nausea and vomiting. Physical examination showed distention of the veins of the neck and moist rales at the left-lung base. The heart was not enlarged. The pulmonic second sound was greater than the aortic. An ill defined precordial systolic murmur was audible. There was +++ pitting edema of the legs and sacrum. The pulse was 142 and irregular. The blood pressure was 162 systolic, 112 diastolic, with 30 mm. of pulsus paradoxus. The white-cell count was 26,200. The serum nonprotein nitrogen was 250 mg., the calcium 5.8 mg., the phosphorus 9.8 mg., the albumin 2.9 gm., and the globulin 1.6 gm. per 100 ml. With digitalis therapy the dyspnea was relieved, the pulse fell from 190 to 100, the pulmonary rales disappeared, and the pulmonic second sound became diminished and less intense than the aortic. An electrocardiogram on the fourteenth hospital day showed atrial fibrillation with a ventricular rate of 130; the QRS interval was 0.07 second; the axis was −15°; Q waves were present in Lead aVR; R waves were low in Leads V_1 through V_3; the T waves were inverted in Leads aVL, V_5 and V_6, and low or diphasic in the other leads. Two weeks later a similar episode was relieved with tourniquets, oxygen and aminophylline. Examination of the heart at this time showed the point of maximal impulse to be at the anterior axillary line in the sixth intercostal space. The blood pressure was 150 systolic, 80 diastolic. A culture of the throat grew out abundant beta-hemolytic streptococci and *Haemophilus influenzae*. A blood culture was negative. Crysticillin therapy was begun. X-ray films showed more hazy density in both lung fields and no further change in the size of the heart. An electrocardiogram showed no significant change. The hemoglobin was 7.3 gm., and the nonprotein nitrogen 320 mg. per 100 ml. In spite of redigitalization with Cedilanid, Digalen and Digoxin, as well as oxygen, tourniquets and Southey tubes, diffuse, coarse, bubbling pulmonary rales became audible, and there was massive peripheral edema. The patient died on the twenty-fifth hospital day.

Differential Diagnosis

Dr. Alfred Kranes*: Some years ago I asked Dr. Castleman if he would refrain from asking me to discuss patients dying of renal insufficiency because I did not feel capable then, and certainly do not now, of predicting the structural changes in the kidneys of such patients. He has honored that request until now. When this protocol arrived on my desk several days ago, I concluded either that he hoped my diagnostic acumen had improved or that some other member of the department, unaware of this agreement, had sent the record.

*Physician, Massachusetts General Hospital.

In any event we are faced with a patient having renal disease and a vast amount of laboratory data, most of which are not helpful to me. In all fairness one must say that the laboratory data were valuable to those who were taking care of the patient since it was their job to treat a physiologic disturbance. My problem is to determine what morphologic changes occurred in the kidney of this patient with rapidly progressive renal disease, which killed him in five months.

There must have been considerable difficulty in abstracting this long record since I find myself uncertain about a number of things that appear in it. Perhaps I may be given some additional information. The temperature on admission was 100.8°F.; nothing further is said about fever, but do the remarks that blood cultures were taken indicate a febrile course?

DR. RICHARD B. COHEN: The patient ran a low-grade fever with occasional spikes and an occasional return to fairly normal temperature — 99 to 100°F. — for several days.

DR. KRANES: The x-ray films of the chest were said to show a diffuse, patchy, homogeneous density; can something be diffuse and patchy and homogeneous? Perhaps Dr. Wang will show the films.

DR. C. C. WANG: The patient had many x-ray examinations of the chest taken during the course of the hospitalizations. The first film, taken at the time of the first admission, shows multiple hazy homogeneous densities in both lung fields, somewhat more on the right. The hilar shadows are unusually large, and the superior mediastinum appears somewhat widened, suggesting lymphadenopathy (Fig. 1).

DR. KRANES: How would you interpret that?

DR. WANG: I think that the patient had a diffuse pulmonic disease.

DR. KRANES: Is it consistent with pulmonary edema?

DR. WANG: It could represent pulmonary edema, but the appearance is not typical; in pulmonary edema I should like to see more centrally located, butterflylike densities.

Approximately six weeks later there was a remarkable clearing of the lung fields.

DR. KRANES: Do you not think, then, that the previous changes had been due to pulmonary edema?

DR. WANG: Yes; I do. The films taken twelve weeks after admission demonstrate definite enlargement of the mediastinal and hilar lymph nodes and clear lung fields. The films of the chest taken on the last admission show reappearance of the pulmonary abnormality; the hilar and mediastinal shadows are unchanged. The heart, however, has progressively enlarged somewhat throughout the course of the observation.

DR. KRANES: The patient, I assume, was too sick to be fluoroscoped.

DR. WANG: The patient was not fluoroscoped.

The films of the abdomen are not remarkable, and the spleen is slightly enlarged.

DR. KRANES: That information clears the problem somewhat.

I am puzzled by what happened after the Meticorten therapy. It appears from this record that after the patient was given Meticorten an enormous diuresis occurred, and the nonprotein nitrogen rose. I suspect that that may not actually have been the case.

DR. ALLAN I. SANDLER: That is correct; the nonprotein nitrogen continued to climb after the diuresis, which occurred shortly after the Meticorten was started.

DR. KRANES: So that the nonprotein nitrogen did continue to rise during the period of diuresis, and returned to a more nearly normal level later.

Toward the close of the first admission, recurrent ascites is noted; yet it had not been mentioned before. Am I to infer that the patient had ascites during much of that admission?

DR. MITCHELL T. RABKIN: He did not have it on admission.

DR. KRANES: It developed, disappeared and redeveloped?

DR. SANDLER: After the Meticorten was administered, fluid began to accumulate; then the intake of fluid was restricted, and the accumulated fluid disappeared.

DR. KRANES: I am also puzzled by the fact that although the blood pressure was normal during the first admission, the patient was discharged taking Serpasil. Perhaps the Serpasil was given as a tranquillizing agent. Was the blood pressure really normal all during the first admission?

DR. RABKIN: No; in the last three weeks of the first admission, the blood pressure reached levels of 160 systolic, 100 diastolic.

DR. KRANES: The failure of multiple transfusions to raise the hemoglobin level must have been due to hemolysis. Although there was no laboratory confirmation of hemolysis, either in elevated urobilinogen levels, a positive Coombs test or reticulocytosis, there seems to be no other logical explanation for the lack of benefit from the transfusions.

During the final admission a cardiac murmur is reported for the first time and is described at different times in different ways. This, along with the pulsus paradoxus, makes me wonder whether the patient had a terminal uremic pericarditis. I see no way of settling that issue unless those who listened to the murmur believed it to be a friction rub.

The logical choices of the type of renal disease in this patient are rather limited. Among the more unlikely possibilities, pyelonephritis has to be mentioned, but not considered seriously because at no time was there any evidence of urinary-tract infection although on the last admission some white cells were found in the urine. Furthermore, the nephrotic syn-

drome is an unlikely accompaniment of chronic pyelonephritis. Among other unlikely causes of the nephrotic syndrome one mentions amyloidosis and thrombosis of the inferior vena cava at the level of the renal vein. One only mentions them, however.

As one reads the history one is impressed by the fact that whereas the nephrotic syndrome was present it was merely an incident in a much more serious underlying disease, so one looks further for the cause of the renal disease.

The most logical explanation of the illness is some disease of the renal blood vessels. To say that this was a disease of the renal vasculature would be a reasonably safe but unacceptable diagnosis. I have to decide, in addition, not only the size of the renal vessels involved — arteries, arterioles or glomeruli — but also in what fashion these vessels were afflicted. Were they wire-loop lesions, inflammatory lesions or degenerative or necrotizing lesions? From here on one must guess.

Of the various vascular diseases afflicting the kidney, nephrosclerosis can be excluded, not only by the clinical course but also by the fact that during the entire first three months of the illness the blood pressure was normal. Among the other types of renovascular lesions, only two need be considered seriously: one is glomerulonephritis, and the other is the mélange of diseases that goes by the name of polyarteritis nodosa. Most of the urinary, blood chemical and cardiac and probably also the pulmonary findings can well be explained on the basis of glomerulonephritis. Certainly, progressive renal disease is not at all unusual. The presence and disappearance of pulmonary edema and cardiac enlargement, probably as a result of terminal uremic pericarditis, offer no insuperable difficulty for that explanation. Glomerulonephritis does not explain well the muscular cramps; nor does it account for the pains in the temporomandibular and shoulder joints, or the dramatic improvement, not only in the symptoms but also in the state of the renal disease, that occurred with steroid therapy.

For these reasons one turns to the diagnosis of polyarteritis nodosa, which more adequately explains not only the renal disease but also these other features. One cannot help being influenced by the statement in the past history that four years before admission, serum sickness developed after horse serum was injected. Perhaps some medication had been given in a routine fashion before the final illness. Horse serum is not commonly used these days, but a sulfonamide or penicillin may have been given for some unmentioned minor infection. If so, the renal lesions may have been those of hypersensitivity angiitis, described by Knowles and others,[1] in which steroid therapy has been helpful. In these cases the predominant lesions are in the glomeruli, although other larger vessels in the body and in the kidneys may be involved. Davson and his co-workers,[2,3] who have also written about this type of renal lesion, call it a necrotizing glomerulitis. They also point out that it may be confined solely to the kidney, although in most of their cases, there were lesions in other organs. It is of considerable interest that in such cases normal blood pressures were frequently encountered. In this patient the cardiac and pulmonary lesions may have been due to diffuse involvement of the pulmonary vessels and perhaps of the coronary vessels. I see no way of deciding that. I favor a diagnosis of polyarteritis nodosa as an explanation of the renal disease.

DR. COHEN: Dr. Ropes, have you a comment?

DR. MARIAN W. ROPES: I saw the patient during the first admission. We, too, tried to decide whether or not he had involvement merely of the vessels of the kidneys and on what basis, or whether other vessels were involved. I think that it is fair to say that the majority opinion was that the diagnosis was glomerulonephritis. However, some of us — and I was one — thought that the definite joint involvement and the other evidence suggestive of vascular disease elsewhere in the body favored a diffuse vasculitis. To attempt to put a name on it was difficult. We considered hypersensitivity angiitis and two of the connective-tissue diseases — polyarteritis nodosa and disseminated lupus erythematosus. I believed that there was probably involvement of vessels outside the kidney and that there was a diffuse vasculitis, undiagnosable.

DR. COHEN: Dr. Kranes, do you believe that the renal lesion was improved under the influence of Meticorten?

DR. KRANES: No; renal function was improved in that the patient was able to get rid of large amounts of fluid.

DR. ROPES: There was even some discussion clinically about whether he was better. I believed that there was little evidence of real improvement on hormone therapy. The point was debated. I think there was slow improvement for two or three weeks, such as one sees in this type of inflammatory disease, and a steady downhill course from then on.

DR. KRANES: The protocol described a dramatic improvement.

DR. COHEN: That was to a considerable extent based on the subjective relief of pain and his generally feeling better rather than upon objective evidence other than loss of edema.

DR. JOHN F. HEGGIE: It was actually more than that; the Meticorten, we believed, kept him from dying.

DR. SANDLER: I do not think that there was any question about it. He lost weight, and kidney function was improved in every sphere: excess water and salt were eliminated from the body, the nonprotein nitrogen decreased, and the creatinine clearance, I believe, went from a low of 4 liters to about 65 liters per twenty-four hours. From the beginning of the

Meticorten therapy there were no fresh hemorrhages in the retina, which had continued to develop after admission in the absence of hypertension. Only in the first few days did they appear along with the arthritic involvement and the gastrointestinal symptoms, which were out of proportion to the uremia at that time. The disease overwhelmed him two months later, and he went progressively downhill from that point on.

DR. KRANES: Why did you give him Meticorten?

DR. SANDLER: We hoped that there was a hypersensitivity angiitis. I think most of the physicians caring for him thought that he had vasculitis.

CLINICAL DIAGNOSIS

Vasculitis.

DR. ALFRED KRANES'S DIAGNOSIS

Polyarteritis nodosa.

ANATOMICAL DIAGNOSES

Disseminated arteritis and arteriolitis, probably secondary to hypersensitivity, with acute and chronic necrotizing glomerulitis.

Cardiomegaly, hypertensive type.

Bronchopneumonia, confluent, partially organized. (Uremia.)

Hydrothorax, bilateral.

PATHOLOGICAL DISCUSSION

DR. COHEN: At autopsy the body was that of a well nourished man. There was bilateral hydrothorax. The lungs were diffusely edematous, with generalized bronchopneumonia.

The most striking gross pathologic process was in the kidneys, which were large and pale, with surfaces dotted by petechial hemorrhages. This appearance is not specific but suggests acute glomerulonephritis, malignant nephrosclerosis without a marked chronic component or certain types of arteritis as suggested by Dr. Kranes. On microscopical examination almost every glomerulus in numerous sections was found to be enmeshed by an inflammatory process, which ranged from active infiltration with well preserved neutrophils to extensive necrosis with complete or partial loss of glomerular structure. The chronicity of the process was attested to by numerous glomeruli undergoing fibrotic healing. Crescents, which are a histologic feature of exudative inflammation in the glomerulus, were frequently seen. Associated with this glomerular disease was an extensive necrotizing arteriolitis and arteritis, with fibrinoid necrosis and focal thrombosis (Fig. 2). Evidence of fibrous healing in vessels was noted. The large renal vessels were normal. Similar vascular lesions were found throughout the body, with particularly severe involvement of peripheral nerve (Fig. 3), spinal ganglion, skeletal muscle and testicle. The lung and central nervous system showed no arteritis.

The acuteness of some of the lesions leave little doubt that new arteritic lesions were developing while the patient was receiving Meticorten. There is suggestive evidence, both clinical and pathological, that cortisone may act adversely in certain cases of arteritis.[4,5] It apparently acts to produce rapid fibrous obliteration of affected arteries, with resultant tissue ischemia and perhaps the rapid onset of a severe hypertension. This, of course, must be balanced against the many cases that were reported as showing a salutary effect of steroid therapy.

Dr. Kranes was correct in his diagnosis of a necrotizing arteritis, associated with renal lesions resembling an acute necrotizing glomerulonephritis of a type previously described by Davson and others.[2,3] This case, then, belongs to the group of diffuse vascular lesions that Dr. Kranes has aptly called a "mélange," which have been grouped both clinically and pathologically under the heading of polyarteritis nodosa. On the basis of the clinical picture, possible

FIGURE 2. *Photomicrograph of the Kidney.*
Note the arteriole, showing extensive fibrinoid necrosis of its wall, with infiltration of neutrophils and lymphocytes into the wall and into the periarteriolar tissue. A glomerulus (arrow) is more chronically affected with fibrosis and capsular adhesions.

etiology, distribution of lesions and certain distinctive morphologic features attempts have been made to arrange these cases into a variety of subgroups. These range pathologically from the classic group described by Kussmaul and Maier in the mid-nineteenth century, with involvement of large and medium-sized vessels and macroscopic nodular arteritis, to the allergic granulomatous arteritis emphasized recently by Churg and Strauss[6] and the "hypersensitivity" arteritis

discussed by Zeek et al.,[1,7] which involves small arteries, arterioles and sometimes veins. Although some overlapping is probably present and the subgroups may not be sharply defined, it is probably of value for both pathologist and clinician to attempt the distinction.

FIGURE 3. *Small Artery Supplying a Peripheral Nerve, Showing Severe Necrosis and Neutrophilic Infiltrate into the Wall of the Vessel and on the Surrounding Tissue.*

Multiple mechanisms of etiology certainly exist. It is well known that generalized arteritis may be the result of hypersensitivity to a great variety of substances.[7] Hypertension produced experimentally may also result in generalized arteritic lesions.[8] Other types of arteritis exist in association with specific pathologic complexes — that is, rheumatic and rheumatoid — or as more isolated focal lesions — that is, temporal arteritis and giant-cell aortitis.

In this case the history of serum sickness, the localization of the pathologic process in small vessels and the relatively late onset of hypertension favor hypersensitivity as an important etiologic factor. However, as in most of these cases, the substance or substances to which the patient was sensitive and the associated contributory factors necessary to make the reaction take this particular form are unknown.

DR. KRANES: Davson et al.[2,3] state that one can recognize these kidneys grossly. Do you agree?

DR. COHEN: As I mentioned previously, I should rather not make an absolute diagnosis on gross examination; I should prefer to consider it as one of several entities until the microscopical sections are examined.

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FREEDOM OF THE PRESS IN BRITAIN

An interesting sequence of events that took place this spring and summer reveals the regard in which the British doctor holds the official journal of his association and also, perhaps, the veneration in which the average enlightened Briton, jealously guarding the traditional independence of his kind, holds the freedom of the press.

It all began with a leading article in the *British Medical Journal* of April 7 entitled "The Gold-Headed Cane" — historic symbol of the Royal College of Physicians. In firm but kindly spirit the editorial writer indicated the apparent eagerness of the College to enter into medicopolitical affairs but its confusion in respect to the methods by which its influence should be made felt. Especially odd to the writer appeared its refusal to join with the British Medical Association in considering problems of medical education. The editorial raised the question whether it is wise to continue a president in office for seven years, and whether the College, basking in its storied glory, is responding adequately to the challenge of the times, or whether its function has come to be merely that of custodian of the historic cane. It strongly implied that other of the venerable colleges, societies and corporations of Great Britain have become more than associations for mutual admiration but that the College of Physicians walks too literally with dependence on its famous staff.

A week later the *Journal* published a rebuttal by Sir Russell Brain, president of the College, to the effect that his organization is co-operating with the current government, whereas the British Medical Association and its journal are the ones that vacillate. Moreover, according to Sir Russell, the royal colleges and similar institutions should remain free to express their independent views (somewhat after the manner of a loyal opposition). Following Sir Russell's retort came a brace of messages congratulating the *Journal* on its stand.

More, however, was to come, for not only had the *Journal* committed a sort of lese majesty in its comments on a subject of such delicacy; it had done so to the apparent embarrassment of elements within the ranks of the Association itself. This was brought out at the Annual Representative Meeting of the Association at Brighton in July, reported in the Supplement to the *British Medical Journal* of July 14, when high praise of the *Journal* and its distinguished editor, Dr. Clegg, was delivered by the chairman of the Journal Committee, followed by a motion presented by Mr. Langston, of Winchester,

> That this Representative Body instructs the Council to take steps to ensure that leading articles in the *British Medical Journal* reflect the policy of the Association.

In the discussion that ensued, a strongly developed conviction made itself felt that the position of the editor of the *Journal* entitled him to the expression

of his honest opinions. In the word of one speaker, it would be a tragic day for the Association when the editor, writing an article, had to ask the Council in advance for its policy. Two things that must be protected at all costs by the Representative Body are its freedom of speech in assembly and the freedom of expression of opinion in its *Journal*.

The points were brought out that the editor is engaged by and is subject to the control of the Council; that he is responsible for all the matter printed in the *Journal* except for announcements and material that he is instructed by the direction of the Council to publish and that, within the framework of the general policy known to be that of the Representative Body he is expected to discharge his duties as an independent and trusted agent. If he is incapable of so functioning, or if he is consistently antagonistic to the policies of his association, then he should be replaced by an editor of greater capacity or sweeter reasonableness. In the case of the leading article in which the Royal Society of Medicine was criticized, no policy on the part of the British Medical Association existed — except that of the right to criticize — and so none was violated.

The restrictive motion was then defeated by an overwhelming majority, a mark not only of the Englishman's devotion to self-determination in the conduct of his own affairs, but of the high personal regard in which the editor of the *British Medical Journal* is held by his colleagues.

Freedom of the press, like many freedoms, is one of the two-edged tools that especially pertains to democracy. Like others it can cause grave injury when misused. The personal element must often be the safeguarding factor — to have it in hands as capable and as responsible as those of Dr. Clegg.

Without freedom the press is ineffective as an expression of democracy; without capable leadership it may become an irresponsibly directed or a blunted weapon. Freedom of the press is a political guarantee with which freedom of the editor in respect to the publication for which he is responsible should not be confused. The first is guaranteed by the form of government under which it exists; the second is an indefinable relation dependent on the understanding that exists between the editor and his publishers. If the publishers are conscious of their responsibility in maintaining a free press and the editor is worthy of their confidence he will be given a free hand in the conduct of the publication and in the development and expression of editorial opinion. It is such a position that the editor of the *British Medical Journal* so justly occupies in the organization of the British Medical Association.

SYPHILIS RESURGENT

Treponematosis probably originated several hundred thousand years ago in the hot humid region of Central Africa, whence it was conveyed by human migration to Asia.[1] Yaws, the modern counterpart of this earliest treponematosis, is propagated under the conditions of primitive village life. As treponematosis extended northward to the temperate zone it developed into various forms of endemic syphilis such as bejel. Venereal treponematosis — known today as syphilis — appeared as mankind developed urban life, and since then has always been present. Spread by sexual promiscuity, it has wrought havoc on individuals, families and nations.

Until the dawn of the chemotherapeutic era, two factors alone determined the incidence and prevalence of syphilis: the size of the infectious reservoir in the community and the sexual mores of its people. With chemotherapeusis came another factor affecting the degree of spread. Ehrlich, with his magic weapon, salvarsan, in 1907 spearheaded the beginning of modern methods of venereal-disease control. The Wassermann test had been developed in the previous year, after the discovery in 1905 of the causative organism, *Treponema pallidum,* by Schaudinn and Hoffmann. Methods were now available for confirming a clinical diagnosis and for screening a population without clinical lesions. Most important, there was an effective although somewhat primitive method of treatment.

The years brought improvement in methods of laboratory diagnosis, notably refinements in the Wassermann test, and the development of cardiolipin antigen. The fundamental studies of Michaelis in 1907 led to the flocculation tests, which were in general use by 1922. In 1949 came the treponema-immobilization test of Nelson and Mayer and, in 1955 the complement-fixation test for *T. pallidum*.

Time also brought newer and safer means of treatment to the medical world: neo-salvarsan in 1912, malaria therapy in 1917, bismuth in 1921, arsenoxide in 1933 and last, but most important, penicillin in 1943. Then, almost in anticlimax, the wide-spectrum antibiotics were found to be effective in the treatment of syphilis, although slightly less so than penicillin.

Coincidental with the discovery of the arsenicals, bismuth and the antibiotics, and particularly since 1936, there was a concerted attempt on the part of clinical and public-health medicine to control syphilis. Clinics were organized for the speedy diagnosis and treatment; physicians were bombarded with propaganda alerting them to the possible presence of this disease, and instructing them in diagnosis and treatment. This concerted effort and the speed and efficiency of penicillin have been responsible for the precipitous fall of primary and secondary syphilis and for the lesser decline of late and congenital syphilis throughout the United States. For example, there was a decrease in primary and secondary syphilis from 107,716 cases in 1947 to 6698 in 1955. Infectious syphilis — that is, the primary, secondary and early latent stages — decreased in the same period from 219,230 cases to 28,930. Late latent and late syphilis, however, declined only from 124,274 cases to 86,392.[2]

This remarkable achievement led many physicians to forget how it was accomplished — it was another

example of "The war is over, let's go home." Maintenance-control efforts were abandoned in many states. In others, control programs were de-emphasized or amalgamated (a catchall connotation). Some physicians forgot syphilis in their differential diagnosis — sometimes much to their embarrassment. To cap it all, the Board of Commissioners of the Joint Commission on Accreditation of Hospitals, at its meeting on January 28, 1956, stated, "The requirement that all patients on admission have a serological test for syphilis has been dropped. This is now optional with the hospitals."[3]

Many thoughtful physicians cautioned against premature rejoicing that syphilis was no longer a problem. Modern control methods cannot eradicate syphilis — they are not geared to it; at best they can only keep it down to the irreducible minimum since they rely solely on early diagnosis and treatment.[4] Never in the history of medicine has any infectious disease been treated out of existence.

Throughout the national decline in reported syphilis the rates of gonorrhea stood out like a warning red beacon. This disease, which responds to one injection of penicillin and is contracted sexually as is syphilis, maintained essentially the same rates. Here and there throughout the country scattered epidemics of syphilis were reported. Then, during the first nine months of the current fiscal year (July 1, 1955, through March 31, 1956), more cases of primary and secondary syphilis were reported in the United States than in the corresponding period of the preceding year. This increase represents a significant upward shift from the national trend line. Although the actual numbers involved are not yet alarming, this upsurge represents a loss of control efficiency for the first time since 1947. This statistically significant reversal of downward trend can only mean that the control effort at its present level is unable to cope with the national problem of syphilis. Since the increases occurred among both sexes, were found in 20 widely scattered states, appeared among both Negroes and whites, and were characteristic of private as well as public treatment sources, they may well forecast large-scale increases in infectious syphilis throughout the nation.

Massachusetts has long been considered an area of low syphilis prevalence. However, in 1951 a 20 per cent increase in syphilis was reported, principally in latent and late stages. These reported rates continued without significant changes at this elevated level until the present fiscal year, when another and sharper increase was observed. As in the nation, there was a significant increase in reported primary and secondary syphilis in fiscal 1956 — 59 per cent over the previous year. Early latent syphilis rose by only 14 per cent; thus, the over-all rise in infectious syphilis — primary, secondary and early latent stages — was 30 per cent; late latent and late syphilis increased by 17 per cent.

The years of complacency are bearing bitter fruit.

References

1. Hudson, E. H. Treponematoses — or Treponematosis? *Current Lit. on Ven. Dis.* Special issue. 1956. P. 56.
2. *V.D. Fact Sheet No. 12.* December, 1955.
3. Babcock, K. B. Standards amended for hospital accreditation. *Hospital Management* **81**:45, 1956.
4. Fiumara, N. J. Venereal diseases — present and future. *Am. J. Pub. Health* **43**:1443-1451, 1953.

THE OLD-SCHOOL TIE

A COMPILATION by the American Medical Education Foundation of contributions by physicians to medical education in the United States during 1955 reports donations to 82 medical schools amounting to $2,505,750.75. Of this sum, $100,000 was a grant from the American Medical Association, and $6,511.67 came from interest on securities, leaving $2,399,239.08 actually given by 61,278 individual contributors, 25,116 physicians contributing $650,651.62 through the Foundation and 36,162 contributing $1,748,587.46 directly to schools, largely as the result of alumni campaigns.

This indicates that the average gift in 1955 by an alumnus to his own school was $48.35, whereas the average gift by a physician to the Foundation (whether or not designating his own school as beneficiary) was only $25.91. The alumni campaigns thus were successful in obtaining individual gifts 87 per cent greater in amount than those made through the Foundation.

In the light of these figures, the Council of the Massachusetts Medical Society probably acted wisely in rejecting a proposal to assess every member to ensure universal participation in the campaign of the American Medical Education Foundation. The figures also show that whereas only 85 Massachusetts physicians contributed to 20 schools through the Foundation, 2535 contributed directly to the alumni funds of 42 schools. The number of schools benefiting from direct contributions was more than twice the number reached through the Foundation.

It seems reasonable to conclude that the Foundation might serve its purpose more effectively if it confined its efforts to helping the schools collect money from their own alumni, and studied the most efficient methods of planning alumni campaigns, rather than acting as a collecting and distributing agency or issuing direct appeals for money.

. . . the amount of solid silver in each bottle of the hair dyes of Ballard, Phalon, Batchelor, Christodaro and Clirehughs, is 10 cents for the first two and 8 cents for the others. All these are sold at one dollar per bottle, leaving an enormous profit. The quantity of silver thus subtracted from the currency is very large. One firm in Buffalo used last year (in a period of thirteen months), 1100 ounces of silver coin.

Boston M. & S. J. *August 21, 1856*

MASSACHUSETTS MEDICAL SOCIETY

DEATH

RYAN — Terrence C. Ryan, M.D., of Springfield, died on July 6. He was in his fifty-ninth year.

Dr. Ryan received his degree from Harvard Medical School in 1924. He was a member of the staffs of Mercy, Wesson Memorial and Municipal hospitals and a fellow of the American Medical Association.

He is survived by his widow and two sons.

MASSACHUSETTS DEPARTMENT OF PUBLIC HEALTH

LABORATORIES APPROVED FOR STANDARD SEROLOGIC TESTS FOR SYPHILIS

This year 46 laboratories have been approved for the performance of standard diagnostic tests for syphilis.

Legally, only these laboratories and the Department of Public Health Wassermann Laboratory may perform the premarital blood tests prescribed by law in this state. The Wassermann Laboratory, 281 South Street, Jamaica Plain, is the only laboratory in Massachusetts whose reports are recognized in other states for premarital purposes.

The laboratories approved for the tests required by law are as follows:

Attleboro:
Sturdy Memorial Hospital

Boston:
Boston Dispensary
Boston Health Department
Commonwealth Clinical Laboratory
Leary Laboratory
Massachusetts General Hospital
Massachusetts Memorial Hospitals, Genito-Infectious Disease Clinic
James Quinn Laboratory

Brockton:
George E. Bolling Laboratory, Health Department

Brookline:
Sias Laboratories

Clinton:
Clinton Hospital

Fall River:
St. Anne's Hospital
Union Hospital

Fitchburg:
Burbank Hospital

Framingham:
Framingham Union Hospital

Gardner:
Henry Heywood Memorial Hospital

Great Barrington:
Fairview Hospital

Greenfield:
Franklin County Public Hospital

Haverhill:
Haverhill Municipal (Hale) Hospital

Holyoke:
Holyoke Hospital
Providence Hospital

Lawrence:
Clover Hill Hospital
Lawrence General Hospital

Lowell:
Lowell General Hospital

Ludlow:
Ludlow Hospital

Methuen:
Bon Secours Hospital

Montague:
Farren Memorial Hospital

New Bedford:
Burt Clinical Laboratory
Professional Laboratory
St. Luke's Hospital

Newton:
Newton-Wellesley Hospital

North Adams:
North Adams Hospital

Norwood:
Norwood Clinical Laboratory

Pittsfield:
Hillcrest Hospital
Pittsfield General Hospital

Quincy:
Quincy City Hospital

Springfield:
Mercy Hospital
Springfield Hospital

Stoneham:
New England Sanitarium & Hospital

Taunton:
Morton Hospital

Tewksbury:
Tewksbury State Infirmary

Waltham:
Waltham Hospital

Worcester:
Department of Public Health
St. Vincent Hospital
Worcester City Hospital
Worcester Hahnemann Hospital

CORRESPONDENCE

SALICYLATES FOR URINARY CALCULI: A WARNING

To the Editor: On the basis of recently published reports such as those of Prien and Walker, entitled "Salicylate Therapy of Recurrent Calcium Urolithiasis" (*New Eng. J. Med.* **253**:446-451, 1955) and "Salicylamide and Acetylsalicylic Acid in Recurrent Urolithiasis" (*J.A.M.A.* **160**:355-360, 1956), various drug companies are currently conducting an extensive mail campaign advertising their particular brands of salicylates for prevention and treatment of urinary calculi. It should be pointed out that this group of drugs was recommended for use *only* in the presence of *calcium*-containing calculi. Their use in the management of patients with recurrent uric acid calculi is contraindicated because of the well known property of salicylates to increase the urinary excretion of uric acid. Before salicylate therapy is begun every effort should be made, including stone analysis, to determine the chemical nature of the calculi being formed.

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GEOGRAPHIC ERROR

To the Editor: The June 7 issue of the *Journal* contains an original article and an editorial on histoplasmosis. Each of these refers to a previous original article by French, Jillson and Crispell appearing in the *Journal* (**249**:270-272, 1953). Both the article and the editorial in the June 7 issue contain an inaccuracy. Perhaps you have already heard from Drs. French et al. about the errors, which should be noted to prevent future writers from perpetuating a mistake or mistakes.

On page 1053 of the article "Disseminated Pulmonary Calcifications" by Drs. Joress and Bushueff in the June 7 issue there is the following sentence: "We postulate that the patient, a native Vermonter who had never left his home state, inhaled the spores of *H. capsulatum* while he was cleaning out chicken houses as a part of his daily chores."

The editorial on page 1100 of the same issue states: "A case of histoplasmosis in a native Vermonter who had never been outside New England was reported in the *Journal* in 1953 . . ."

Reference to page 272 of the article by French et al. in the August 13, 1953, issue of the *Journal* shows that the patient had spent his entire life in New Hampshire and

Vermont except for driving to Boston on four or five occasions, motoring to New York City for an overnight trip and for an automobile trip to the Trudeau Sanatorium in New York, where he was a bed patient for six weeks before returning to Vermont by car. The patient, therefore, not only had been out of Vermont but also had been out of New England.

These may be minor points, but I think that they should be corrected now; otherwise, the medical literature will permanently record an erroneous geographic limitation.

RENWICK K. CALDWELL, M.D.
Florence, Massachusetts

NONCLINICAL NOTES

MASSACHUSETTS TRUDEAU SOCIETY

At a meeting of the Massachusetts Trudeau Society the following officers were elected for 1956-57: president, Dr. Edward J. Welch; vice-president, Dr. Norman J. Wilson; secretary-treasurer, Dr. Kenneth T. Bird.

NOTICES

RHODE ISLAND MEDICAL SOCIETY

The trustees of the Caleb Fiske Fund of the Rhode Island Medical Society announce that the subject of this year's prize essay will be "The Present Day Treatment of Infertility." The dissertation must be typewritten and double spaced, should not exceed 10,000 words and must be submitted by January 10, 1957. A cash prize of $350 is offered.

Further information may be obtained from the Secretary, Caleb Fiske Fund, Rhode Island Medical Society, 106 Francis Street, Providence 3, Rhode Island.

VERMONT HEART ASSOCIATION AND UNIVERSITY OF VERMONT COLLEGE OF MEDICINE

A symposium on the subject "Electrolytes and the circulation," under the joint sponsorship of the Vermont Heart Association and the University of Vermont College of Medicine, will be held at the college, Burlington, Vermont, on September 8 (afternoon), September 9 (all day) and September 10 (morning).

The symposium will be devoted to electrolyte metabolism in congestive heart failure and the role of electrolytes in myocardial metabolism, the electrocardiogram and cardiac arrhythmias and vascular reactivity and hypertension.

Further information may be obtained from Dr. Eugene Lepeschkin, University of Vermont College of Medicine, Burlington, Vermont.

SAN DIEGO POSTGRADUATE ASSEMBLY

The tenth annual postgraduate assembly of the San Diego County General Hospital will be held at the County Hospital on September 19 and 20, 1956.

AMERICAN COLLEGE OF CHEST PHYSICIANS POSTGRADUATE COURSES ON DISEASES OF THE CHEST

The Council on Postgraduate Medical Education of the American College of Chest Physicians is offering the following Postgraduate Courses on Diseases of the Chest.

The eleventh annual postgraduate course to be held at the Hotel Knickerbocker, Chicago, Illinois, October 15-19.

The ninth annual postgraduate course to be held at the Park-Sheraton Hotel, New York City, New York, November 12-16.

Further information may be obtained from Murray Kornfeld, Executive Director, American College of Chest Physicians, 112 East Chestnut Street, Chicago 11, Illinois.

INTERNATIONAL CONGRESS OF OTOLARYNGOLOGY

The deadline for submitting titles of papers and films for presentation at the Sixth International Congress of Otolaryngology is October 1, 1956. Requests for places on the scientific program must be received before that date together with an eight-hundred-word abstract of the paper. Applications and abstracts should be sent air mail to the General Secretary, 200 N. Michigan Ave., Chicago 11, Illinois.

SOCIETY MEETINGS AND CONFERENCES

AUGUST 19–23. American College of Chest Physicians. Page 840, issue of November 10.
AUGUST 24 and 25. National Hemophilia Foundation. Page 249, issue of August 2.
AUGUST 27 and 28. Consultation Clinics for Crippled Children in Massachusetts. Page 1244, issue of June 28.
SEPTEMBER 3–5. Congress on Blood Transfusion, Blood Banks and Hematology. Page 297, issue of February 9.
SEPTEMBER 3–7. First Inter-American Conference on Occupational Medicine and Toxicology. Page 152, issue of July 19.
SEPTEMBER 8, 9 and 10. Vermont Heart Association and University of Vermont College of Medicine. Notice above.
SEPTEMBER 9–13. International College of Surgeons. Page 304, issue of August 9.
SEPTEMBER 19–20. San Diego Postgraduate Assembly. Notice above.
OCTOBER 7, 8 and 9. New Hampshire and Vermont State Medical Societies. Page 304, issue of August 9.
OCTOBER 8–13. International Cancer Cytology Congress. Page 104, issue of July 12.
OCTOBER 15–19. American College of Chest Physicians. Postgraduate Courses on Diseases of the Chest. Notice above.
OCTOBER 15–26. New York Academy of Medicine. Page 304, issue of August 9.
OCTOBER 19 and DECEMBER 14, 1956, and FEBRUARY and APRIL, 1957. Massachusetts Society for Research in Psychiatry. Page 56, issue of July 5.
OCTOBER 30 and 31 and NOVEMBER 1. New England Postgraduate Assembly, Boston.

CALENDAR FOR THE WEEK BEGINNING THURSDAY, AUGUST 23

THURSDAY, AUGUST 23

*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*8:00–9:00 a.m. Surgical Grand Rounds. Dr. John Spellman and staff. Saint Elizabeth's Hospital.
*8:45–9:45 a.m. Cardiac Grand Rounds. Jimmy Fund Building. Children's Medical Center, 35 Binney Street.
*9:00–10:00 a.m. Surgical Rounds. Sherman Auditorium, Beth Israel Hospital.
*9:00–10:00 a.m. Arthritis Grand Rounds. Robert Breck Brigham Hospital.
*10:00–11:00 a.m. Combined Medical-Surgical Rounds. Sherman Auditorium, Beth Israel Hospital.
10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by Members and Guests of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*11:00 a.m.–12:00 m. Pediatric Conference. Mount Auburn Hospital.
*11:00 a.m.–12:00 m. Medical Grand Rounds. Dr. Sylvester McGinn and staff. Saint Elizabeth's Hospital.
*11:00 a.m.–12:00 m. Medical Staff Conference. Sherman Auditorium, Beth Israel Hospital.
*11:00 a.m.–12:30 p.m. Hand Clinic (Physical Medicine and Rehabilitation Service). Boston City Hospital.
*12:15–1:15 p.m. Tumor Clinic. Dr. T. W. Botsford. Amphitheater, Peter Bent Brigham Hospital.
*3:00 p.m. Thoracic Conference. The Role of Assisted Ventilation in the Treatment of Chronic Pulmonary Disease. Dr. Thomas K. Burnap.

FRIDAY, AUGUST 24

*8:00–8:45 a.m. Case Presentations. Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*8:00–9:00 a.m. Members and Guests of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*9:30–11:30 a.m. Medical and Surgical Grand Rounds. Drs. George W. Thorn and Francis D. Moore. Main Amphitheater, Peter Bent Brigham Hospital.
*10:00 a.m. Tuberculosis Surgical Clinic. South End Health Unit, 57 East Concord Street.
10:30–11:15 a.m. Lecture on Diabetes for Doctors and Patients by Members and Guests of the Joslin Clinic. Joslin Auditorium, New England Deaconess Hospital.
*12:00 m. Urological Conference. Dr. C. J. E. Kickham, presiding. Auditorium, Carney Hospital, Dorchester.
*12:00 m. Pediatric Grand Rounds. Thorndike Amphitheater, Boston City Hospital.
*1:30 p.m. Fertility and Endocrine Clinic. Free Hospital for Women, Brookline.
*1:30 p.m. Tumor Clinic. Mount Auburn Hospital, Cambridge.
*2:00–3:00 p.m. Pathology Conference. Dr. James Graham. Saint Elizabeth's Hospital.
*4:00–10:00 p.m. Alcoholism Clinic. By appointment. Washingtonian Hospital, 41 Morton Street, Jamaica Plain.
*4:30 p.m. Neuroradiologic Conference. X-Ray Conference Room, New England Deaconess Hospital.

(Concluded on page xxxviii)